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FACTORS DETERMINING THE RELATIVE INTENSITY OF THE HEART SOUNDS IN DIFFERENT AUSCULTATION AREAS

AN EXPERIMENTAL STUDY *

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CLEVELAND

I. INTRODUCTION

It is commonly accepted as a fact that the absolute and relative intensities of the two heart sounds not only offer valuable information concerning the dynamic state of the heart muscle, but also serve as a criterion of the pressure conditions in the greater and lesser circuits. This conception, based on plausible physical assumptions and fortified by clinical experience, has, however, received only cursory attention from experimental investigators.

Lewis,[1] in his experimental studies of the recorded heart sounds, tested the effect of raising the arterial pressure by aortic compression, but was unable to corroborate one general idea, viz., that high arterial pressure, per se, is responsible for an accentuation of the aortic second sound. On the other hand, the experiments of Dean and myself[2] indicated that the intensity of the sounds directly recorded from the heart is determined by the dynamic conditions of the circulation. Thus, we found that the vibrations comprising both the first and second sounds increased, not only in amplitude, but also in number of vibrations, when the ventricles increased in vigor and the blood pressure was simultaneously elevated either by the injection of epinephrin, by aortic compression or by asphyxia. These experiments did not determine, of course, whether the increased ventricular activity or the simultaneous increase in arterial pressure was fundamentally responsible for the accentuated sounds; nor was the question of changes in the relative intensity of sounds over different cardiac areas investigated. With such questions, this investigation is concerned.

* From the Physiology Laboratory of Western Reserve University, School of Medicine, Cleveland.

1. Lewis: Quart. J. Med. **4**:241, 1913.
2. Wiggers, C. J., and Dean, Jr., A. L.: Am. J. Physiol. **42**:476 (Feb.) 1917.

II. METHODS OF INVESTIGATION AND APPARATUS

It is possible, by experimental methods, to modify the circulation so that changes in blood pressure are directly due to or occur independent of cardiac activity; it is possible, also, to modify the circulation so that the pressures in the pulmonary and systemic circuits alter in reverse directions. When such changes are produced within short intervals of time, the changes in intensity of sounds over different cardiac areas can be determined by stethoscopic auscultation or recorded by instrumental means.

To accomplish the latter end, two or three receivers, one each over the apex region, the pulmonary area and the aortic area were snugly applied by an elastic band to the shaved thorax of a dog and held in close apposition by anointing the spot with petrolatum. The sound vibrations were then transmitted by rubber tubing to the sound recording capsules described by Dean and myself,[3] or, in some cases, where a third sound was also recorded, to a microphone connected through an induction coil with a string galvanometer. In all of these experiments, the technical procedures carefully explained in my previous communications with Dean[3] were followed.

III. CRITERIA FOR DETERMINING VARIATIONS IN INTENSITY OF RECORDED HEART SOUNDS

The intensity of tones appreciated by the human ear is directly proportional to the force imparted to the tympanum and is therefore dependent upon the amplitude of vibrations, not only, but upon their frequency as well, factors which may be expressed by the formula $Ia = (NA)^2$. It has, therefore, been proposed by Einthoven[4] that the relative intensity of the heart sounds may be computed according to this formula from photographic records and expressed numerically. This was at first attempted in connection with this investigation, but later given up as unfeasible on the following grounds:

1. The heart sounds, as shown most clearly in Einthoven's laboratory by Battaerd,[5] are composed of vibrations which are exceedingly irregular, both as regards their amplitude and period so that no average amplitude or period can be assigned to the sounds.

2. Owing to a loss of energy in transmission of sound waves to the chest wall, the vibrations originating within the heart reach the thoracic wall much reduced in their amplitude. Of these, a variable number have a vibration frequency which is subminimal, in the sense that they

3. Wiggers, C. J., and Dean, Jr., A. L.: Am. J. M. Sc. **153**:666 (May) 1917; also Arch. Int. Med. **22**:28, 1918.
4. Einthoven: Arch. f. d. gesam. Physiol. **120**:31, 1907.
5. Battaerd: Heart **6**:121, 1915.

do not affect the recording membrane at all. When the amplitude of all vibrations increases, the graphically recorded vibrations become greater in number and, consequently, waves with still different vibration periods are added to the sound complexes. If these are considered, the average frequency of the vibrations — composing particularly the first sound — changes in such a way that the suggested computation has no correct relative value in estimating the objective intensity of a sound.

A rougher, but nevertheless a better estimate of the intensity of the sounds and one which more nearly agrees with the auscultatory findings, can be made by comparing the general picture presented by the vibration groups composing each sound. Thus, if the intensity of the sound increases, the amplitude of the whole wave group increases and the total number of vibrations which enter into the sound component becomes greater. If, on the contrary, the intensity of a sound is reduced, not only is the general amplitude of the sound vibrations much smaller, but the number of vibrations entering into its complex is reduced. This, of course, necessitates that a control record of the sounds be taken previous to the time that the circulation is modified by experimental procedures. Inasmuch as the heart sounds of the dog vary greatly in their intensity with the phases of respiration, it is furthermore necessary to make all comparisons during the same respiratory phase. Since the respirations alter their rate and depth, however, during the experimental procedures employed, it is necessary to make all comparisons during the time of expiratory rest.

IV. EXPERIMENTAL PROCEDURE

Animals which were kept evenly anesthetized by morphin and chloretone were placed on their backs. In the earlier experiments records of the vibrations from the right and left second interspaces and from the apex region were simultaneously taken. Inasmuch as it was found, however, that the directional variation of the first and second sound corresponded in the apex region and over the right second interspace, the experiments were simplified by taking only records from the pulmonic and apex regions in the later experiments. In order to preclude possible instrumental irregularities, the additional precaution was taken in the earlier experiments of connecting each area, in turn, with every sound recording capsule used in registration.

As soon as possible after a control of the normal sounds had been recorded, nerves were stimulated or drugs injected, the resulting effect being controlled in a rough manner by a continuous record of the mean carotid pressure recorded on a revolving kymograph. At sufficient intervals, i. e., usually during the onset of an effect, during

its maximum action, during its decline and after normal conditions had been restored, the sound vibrations were again recorded on the photokymograph. The time that these photographic sound records was taken was also indicated underneath the blood pressure on the kymograph through an automatic electrical signal arrangement.

V. EXPERIMENTAL RESULTS AND DISCUSSION

The results now to be analyzed were found to agree in all the separate trials carried out on fourteen different dogs.

1. *The Influence of Heart Rate Changes on the Intensity of the Heart Sounds.* — Inasmuch as many experimental procedures are attended by a change in heart rate, and inasmuch as the rate of the heart varies considerably in auscultated subjects, it was first necessary

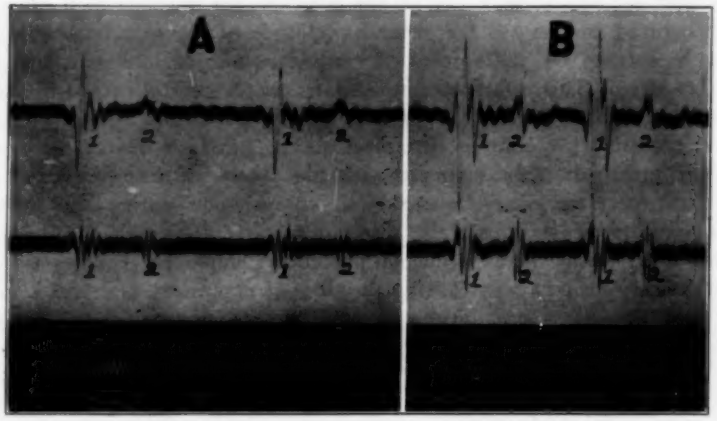

Fig. 1.—(Two-thirds actual size.) Two segments of records showing the change in amplitude of recorded sounds during cardiac slowing, A, during vagus slowing and B, after return to normal rate. Upper record, apex sounds; middle record, pulmonic sounds; lower record, time in 0.02 sec.—1, 2, first and second sound complexes (Experiment C, 210, V).

to study the effect that such primary changes in rhythm produce in the intensity of the heart sounds recorded from different thoracic areas.

In these experiments slowing was induced by mild stimulation of the peripheral end of the vagus nerve; acceleration, either by vagus section or by stimulation of the accelerator nerves.

(a) *The effect of cardiac slowing produced by moderate stimulation of the peripheral end of the vagus nerve.*—The typical effects of mildly stimulating the peripheral end of the vagus nerve are illustrated in the two segments shown in Figure 1. As indicated by the

amplitude and number of vibrations, the intensity both of the first and second sound decreases appreciably over both the pulmonary area and the apex when the heart rate slows.

(b) *The effects of cardiac acceleration produced by vagus section or accelerator stimulation.*—Cardiac acceleration appears to have a variable effect on the intensity of the heart sounds. The first sound is chiefly affected. At times no alteration is apparent, at times, again, an increased amplitude is observed or even a slight decrease may result. Even if allowances are made for the possible shifting of position of the receiving tambours, the results in any given experiment cannot readily be accounted for on experimental grounds.

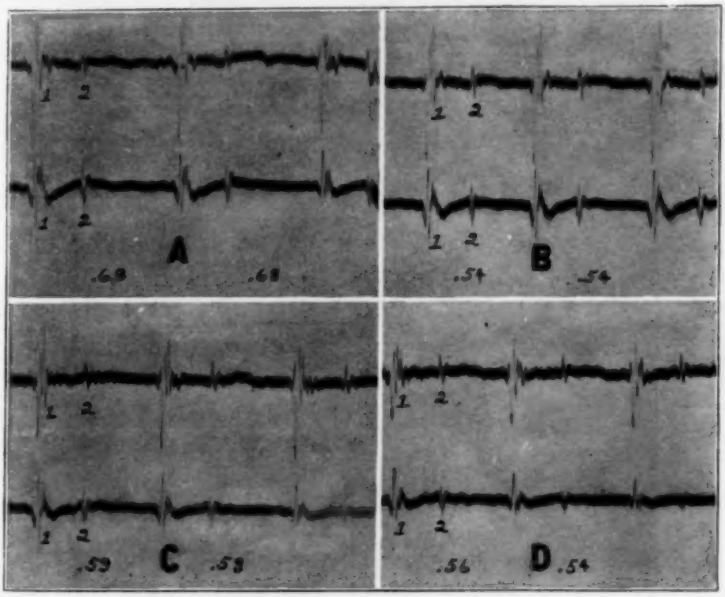

Fig. 2.—(One-half actual size.) Four segments of heart sound records showing effect of cardiac acceleration. Upper record, apex sounds; lower record, pulmonic sounds. Figures .68, .54, etc., marked on curve give duration of heart cycles. Detailed description in text. (Experiment C, 207, III).

In Figure 2, four segments from such an experiment are shown. The first segment, A, is a normal control. The segment, B, shows the sounds after acceleration was produced by section of both vagus nerves. Both sounds at the apex as well as over the pulmonic area are accentuated, as shown both by the larger amplitude and number of vibrations. At the time that the record, C, was taken, the heart had slowed to a slight extent. The first sound is reduced in amplitude in

both curves, the second sound, especially in the pulmonic tracing. Record D was taken during further acceleration of the heart induced by stimulation of the stellate ganglion. All sounds are somewhat reduced over both the apex and pulmonic area.

(c) *Discussion of Results.* — It is common knowledge that when the vagus nerve is stimulated and the ventricles are thus slowed, a fall of the mean systemic and pulmonary arterial pressure results, due to a decrease in the minute volume discharged by the heart. The experiment shows that this fall of pressure, even if moderate, is accompanied by a slight enfeeblement of the second sound; whereas, if the

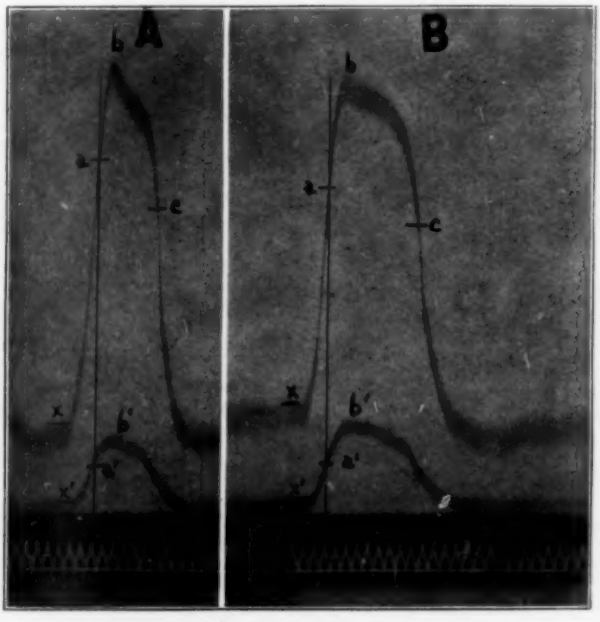

Fig. 3.—(One-half actual size.) Two segments of records showing, left (upper) and right (middle) intraventricular pressure curves. A, normal curves; B, during vagal slowing. Lower curve, tuning fork—50 v.d. Detailed analysis in text. (Experiment C, 216).

pressure drops to any extent, the sounds, both first and second, are diminished in all regions.

Myocardiographic tracings of the ventricles indicate that during vagus stimulation the individual beats are more vigorous and volume curves of both ventricles indicate that the aggregate systolic discharge of the two ventricles increases. We are thus confronted with the

fact that the stronger ventricular beats are accompanied by first sounds of diminished intensity, and we might infer therefrom that the intensity of the first sound is no index of ventricular efficiency.

This unexpected and apparently paradoxical relation led me to reinvestigate the effects of vagal slowing on the right and left intraventricular pressure curves. From such records, it appears that the dynamic effects of continued vagal stimulation are not alike in the right and left ventricles, a fact to which attention has heretofore apparently never been attracted. In Figure 3 are shown two segments of the right and left intraventricular pressures before and during vagus stimulation. The normal pressure curves in the two ventricles may first be considered (A). Owing to the fact that the a-v valves close early in systole, and that the semilunar valves remain closed for an additional short period, each ventricle during its early phase of systole is not able to decrease in volume nor to shorten its fibers; hence the energy of contraction is utilized to develop intraventricular tension. This mode of contraction is spoken of as isometric and consequently

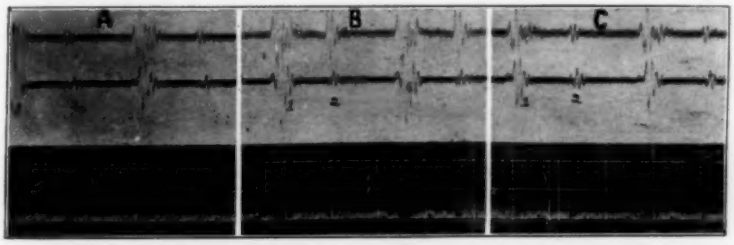

Fig. 4.—(Two-fifths actual size.) Three segments of sound records showing the amplitude of sounds. A, before; B, during central vagus stimulation; C, after return of arterial pressure to normal. Upper record, apex sounds; middle record, pulmonary sounds; lower record (taken by Einthoven's phonocardiographic method), aortic sounds. Abscissae = 0.04 sec. (Experiment C 143, IV).

the interval elapsing before blood is expelled is aptly and concisely referred to as the *isometric period* of systole. This interval extends to the point marked *a* in Figure 3. It is quite obvious upon reflection that the height to which the isometric pressure rises (point a) is determined by the height of the aortic pressure at this time, i. e., the higher the aortic pressure at the beginning of systole, the higher the isometric pressure becomes.

If we compare the right and left intraventricular pressure curves before and during vagus slowing, it is evident that, in the case of the right heart the height of isometric pressure, *a'*, is not greatly altered, while the maximum pressure developed during ejection, *b'*, is dis-

tinctly higher. In the left ventricle, on the other hand, such an effect is very transient, lasting for only one or two beats. After this, as shown in segment B of Figure 3, the height of the isometric pressure, *a*, decreases greatly owing to a falling arterial pressure. The maximum pressure reached during ejection, *b*, is also necessarily somewhat lower. Thus we have a reduction of pressure developed within the left ventricle at the same time that the systolic discharge is distinctly increased.

The reduction in the intensity of the first sounds makes it apparent that the loudness of the first sound is related, not so much to the efficiency of the ventricle as a pumping mechanism as it is to the intracardiac tension developed; and especially to the tension developed before the semilunar valves open. This accords entirely with the observations previously made by Dean and myself,[2] viz., that the vibrations of the first sound reach their maximum intensity before the ejection period has begun, i. e., during the isometric interval.

Cardiac acceleration produced either through double vagotomy or by stimulation of the accelerator nerve, should produce precisely

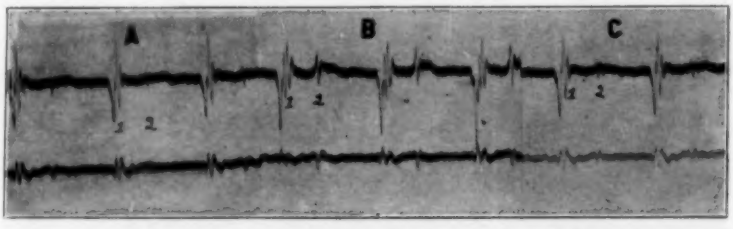

Fig. 5.—(Two-fifths actual size.) Three segments of records showing the amplitude of sounds. A, before; B, during aortic compression; C, after release. Upper curve, apex sounds; lower curve, pulmonic sounds. (C 207, XIII.)

the opposite effect. This result, as shown in the record B of Figure 2, was generally found to be the case. It also harmonizes with the general clinical observation that the first sound is louder in individuals with rapid heart rates. Experimentally, there are, however, distinct exceptions, as shown specifically in the segments C and D of this figure. The cause of this is easily explained. A careful comparison of heart sound records with the simultaneously recorded blood pressure tracings shows without exception that whenever acceleration produces a fair elevation of arterial pressure and an increase in the height of isometric pressure, then the first aortic and apex sounds are also increased. Whenever, through compensatory mechanisms, e. g., reflex dilation, no distinct elevation of arterial pressure occurs and the isometric pressure does not rise above normal, then the first sounds do not alter, or, as is shown in this record, they may even

decrease slightly. These observations establish the fact that changes in heart rate can affect the intensity of the heart sounds only through the attendant dynamic disturbances incurred thereby.

Inasmuch as changes in heart rate are themselves capable of modifying the intensity of the heart sounds, it is obviously necessary to eliminate them, or, at least to take them into consideration in order to evaluate the effect that other circulatory conditions have on the intensity of the sounds. Where heart rate changes occur secondarily through nervous reflexes it is quite possible to eliminate them through the severance of the vagus nerves or paralysis of their terminals by atropin. Certain procedures, however, modify the heart rate through a direct action which cannot be prevented. The foregoing results, viz., that changes in intensity accompanying changes of heart rate are not determined by changes in rate per se, but secondarily by pressure changes induced, are of fundamental help in such instances.

2. *The influence of changes in the total arterial resistance in the intensity of the heart sounds.*—If, as seems probable from previ-

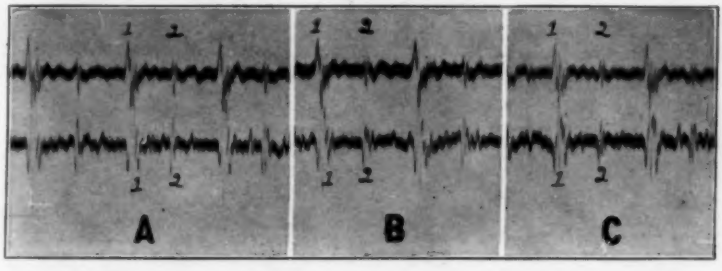

Fig. 6.—(One-half actual size.) Three segments of records showing the relative amplitude of sounds. A, before; B and C, during two stages of pressure decline following injection of sodium nitrite. Upper curve, apex sounds; lower curve, pulmonary sounds (Experiment C 208, X).

ous analysis, the intensity of the heart sounds is fundamentally due to changes in the arterial pressures, and the consequent changes in the height to which intraventricular pressure is elevated during the isometric period of systole, it should be possible to produce such changes without alteration in the heart rate by varying the total resistance against which blood must be pumped. This may be experimentally accomplished in various ways of which the following was utilized in this investigation, viz.: (a) By stimulation of the central vagus which causes a reflex general vasoconstriction. This increases the arterial pressure and, consequently, the height of the left ventricular pressure during the isometric period; (b) by compression of the aorta, which acts similarly, and (c) by the injection of nitrites, which causes a

reduction in arterial resistance, a consequent fall of arterial pressures and a lowering of left ventricular pressure during the isometric interval.

Such systemic changes are not without a secondary effect on the pulmonary and right ventricular pressures. When the total arterial resistance is raised within the arterial system, the left ventricle acts less efficiently as a pumping mechanism and a slight damming back of blood into the pulmonary system occurs. This acts to increase the total resistance in the pulmonary circuit, causes the pulmonary arterial pressure to rise somewhat and increase the pressure in the right ventricle at the end of the isometric period.

(a) *The influence of increasing arteriole resistance by stimulating the central end of the vagus nerve.*—In Figure 4 are shown records before and during the elevation of arterial pressure in this manner. During the elevation of arterial pressure (B) the number and amplitude of the vibrations comprising the first sound increase definitely in all the auscultation areas, indicating an accentuation. In the great

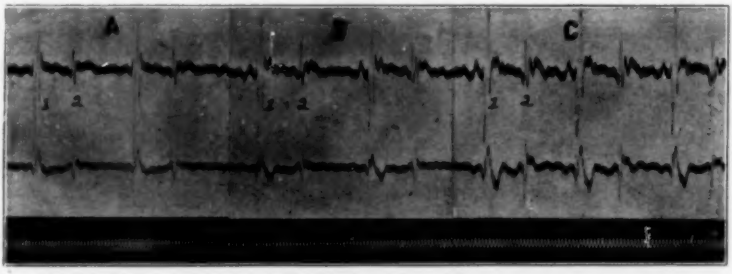

Fig. 7.—(Two-fifths actual size.) Three records of heart sounds showing amplitude of vibrations. A, before; B, during, and C, immediately following rapid saline infusion. The effect started in B continues in C. Upper curve, apex sounds; middle curve, pulmonic sounds; lower curve, tuning fork 0.02 sec. (Experiment C 207, X).

majority of cases, the second sound is also accentuated over the aortic and apex regions, as is well shown in Figure 4. The second pulmonic, though definitely accentuated, increases to a lesser degree.

The relative extent to which the two sounds are accentuated varies greatly in different regions. Over the pulmonary area the first sound is, as a rule, affected most, while over the aortic area, the second sound is predominantly affected. Five minutes after cessation of stimulation (C), the sounds return to normal although the second pulmonic often remains somewhat accentuated.

(b) *The effect of aortic compression on the intensity of heart sounds.*—From a priori considerations we would expect precisely the

same changes in the amplitude of the two sounds as follows central vagus stimulation. As shown in the typical records of Figure 5, this is precisely the case and contrary to the findings of Lewis.[1] The increase in the amplitude of the first as well as the second apical sound is very evident on comparing the second segment (B) with A and C, which are the normal controls before and after compression. While an accentuation of both sounds accompanies a mechanical elevation of arterial pressure, it is quite obvious that the second sound at the apex is accentuated relatively more than the first. In the pulmonic area, the changes in the sounds are not as marked. This is especially true of the first sound, the pulmonary second being somewhat intensified.

(c) *The influence of peripheral dilatation produced by sodium nitrite.* — When sodium nitrite is administered intravenously to an

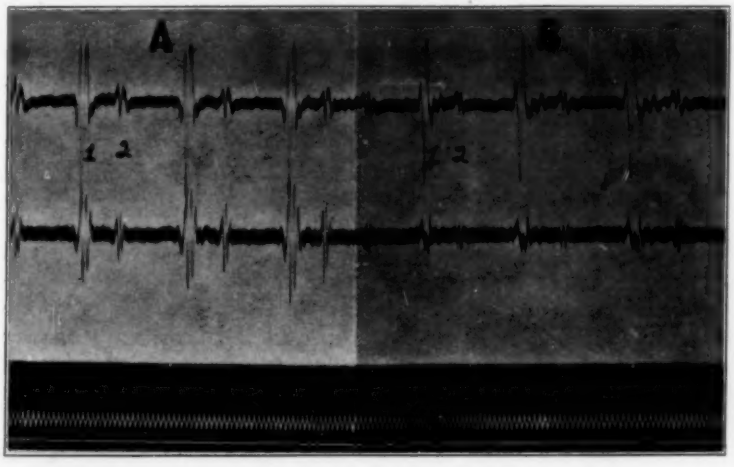

Fig. 8.—(Two-thirds actual size.) Two records of sounds. A, before; B, during compression of the inferior vena cava. Upper record, apex sounds; middle record, pulmonic sounds; lower record, tuning fork vibrations, 0.02 sec. (Experiment C 210, IX).

animal whose vagi nerves have been previously divided, the amplitude of the first and second apex sounds decreases, indicating a reduction in their intensity. A slight, but by no means marked, decrease is also observed in the pulmonary sounds. These changes are well shown in the three segments of Figure 6. Comparison of the relative changes in intensity of the two sounds shows that the enfeeblement of the first sound is greater than that of the second sound.

(d) *Discussion of results.*—These observations confirm the previous conclusion that the intensity of the first sound is related definitely

to the height of the arterial pressure within the pulmonary or systemic circuit and is determined by the height to which the pressure is elevated during the isometric period.

Owing to the fact that the systemic pressure variations are much more extensive in these experiments, they demonstrate much more clearly the relation between the intensity of the second sounds and the height of the arterial pressure. Whenever arterial pressure is raised the second sound augments, and whenever this produces a back effect on the pulmonary circuit, the pulmonary second sound also increases.

It is quite obvious on careful analysis, that the first and second sounds do not always intensify to an equal degree when arterial pressure is raised or lowered through peripheral causes. In the systemic circuit, at least, the rule seems to be that the second sound is predominantly accentuated when the pressure is elevated, while the first is predominantly enfeebled when the pressure is lowered. No explanation entirely satisfactory suggests itself. It is well to bear in mind in this connection that the tension developed during the isometric period, and, consequently, the intensity of the first sound, is determined by the pressure existing at the time that the semilunar valves open (at a, Figure 3). On the other hand, the closure of the semilunar valves is determined by the pressure existing at the very beginning of diastole, e. g., at c, Figure 3. It is quite apparent on reflection that the relative changes of pressure at these two periods may vary independently and to an unequal degree, depending on the particular set of dynamic conditions which operate. Additional work of a very fundamental nature must first be done, however, before a final and satisfactory answer may be given to the question as to why at times the first sound and at times the second sound seems to be affected predominantly.

3. *Influences affecting the systolic discharge of the ventricle.*—Under normal conditions, when the heart rate remains unaltered, the systolic discharge of each ventricle is determined by the volume of blood returning to it during diastole. This also determines the initial pressure (Figure 3, x) which exists within the ventricle at the time it begins to contract, and upon this, in a measure, depends the systolic tension developed within the ventricle itself. By increasing and decreasing the volume of blood returned to the right auricle, it is possible to at once influence the vigor of the right ventricular contraction, and, after a beat or two, also the vigor of the left ventricular contraction.

Such a modification of the venous return may be experimentally produced by the two opposite procedures of (a) rapidly infusing saline solutions into the jugular vein, and (b) clamping the inferior vena cava.

(a) *The influence of rapid saline infusion on the heart sounds.*—Typical sound records of the apex and pulmonary areas before, during and after a rapid saline infusion into the jugular vein are shown in Figure 7, A, B and C, respectively. A comparison of the first sounds in segments A and B indicates that the first sounds are not increased during the course of the infusion when the right heart becomes extremely distended; in fact, the pulmonic first sound may become decreased in amplitude. This is possibly accounted for by the cardiac slowing which is evident. While the mean arterial pressure elevates during infusion, the arterial pressure at the beginning of ventricular ejection is not changed. The reduction of the pulmonary second sound is further influenced by the predominant dilation of the right heart which occurs at the same time.

After injection had ceased, when the heart had recovered its normal rate and dilation was less marked, segment C was recorded. The first

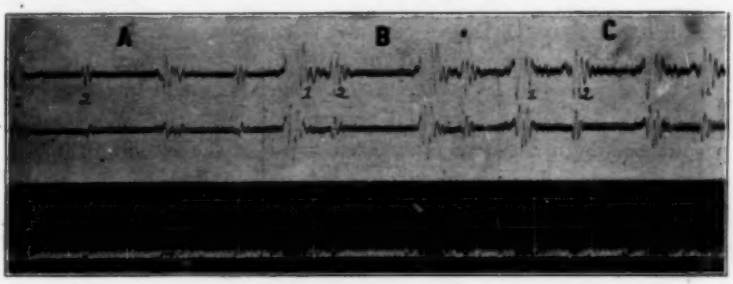

Fig. 9.—(Two-fifths actual size.) Three records showing the relative amplitude of sounds. A, before; B and C, during action of epinephrin. Upper record, apex sounds; middle record, pulmonic sounds, lower record, aortic sounds by Einthoven's phono-cardiograph. Time, abscissae = 0.04 sec. (Experiment C 143, VII).

sound now, true to our anticipation, increases at the apex, and even to a greater extent over the pulmonary area.

The second apical sound, as also the second aortic, increased appreciably in amplitude and number of vibrations as the pressure continued to rise during the infusion. Especially striking, however, is the amplification of the second pulmonic sound. It is noteworthy, also, that during and following such an infusion both pulmonic sounds are affected much more than the aortic or apical sounds.

(b) *The influence on the heart sounds of compressing the inferior vena cava.*—The changes of the heart sounds, before and during compression of the inferior vena cava, are illustrated in Figure 8. While the first and second sounds are both slightly reduced over the apex —

the marked reduction occurs in both pulmonic sounds. These and the preceding experiments where predominant changes in the right ventricle and lesser circulation are evidenced by the greatest variation in the pulmonic sounds are fundamentally important in that they give definite experimental proof (1) that the sounds heard over the left second interspace are really propagated from the pulmonic circuit and right heart, and (2) that valuable information regarding the dynamic conditions of the pulmonary circuits may be gained by comparing from time to time the relative intensities of the heart sounds over different areas.

4. *Influences simultaneously affecting the systolic discharge and total arterial resistance.*—A combination of the cardiac and peripheral factors before studied separately may be induced by intravenous injection of epinephrin into an animal whose vagi nerves have been cut or the terminals of which have been paralyzed by atropin.

(a) *Influence of epinephrin on the heart sounds.*—The changes in the heart following changes in the circulation after injection of epinephrin are very constant. Typical tracings are shown in Figure 9. It is quite evident that the amplitude of the first sound increases to a pronounced degree in all areas. The second sounds are also intensified, but not equally in all areas; the accentuation of the second aortic and of the second apex sound being greater than that of the second pulmonic.

(b) *Discussion.*—Owing to a stimulating effect on the ventricular mechanism, epinephrin causes a greater discharge from each ventricle. This, together with the cardiac acceleration (when the vagi are cut) causes an elevation of the pulmonary arterial pressure and consequently of the right ventricular pressure during the isometric and ejection phases not only, but also produces a higher pressure at the beginning of diastole, i. e., when the semilunar valves close. This accounts for the accentuation of both pulmonic sounds.

In the systemic circuit it causes, in addition, peripheral constriction, which, together with increasing cardiac discharge, causes an enormous elevation of systemic pressure at the end of systole. It may therefore be anticipated that the intensity of the second apex or aortic sound will be very much more augmented than that of the second pulmonic sound. This, as has before been pointed out, proves to be the case.

5. *Influences modifying pulmonary and arterial pressures in opposite directions.*—Finally, it is of great interest to study the relative intensities of sounds from different areas when the pressures in one circuit rise and in the other fall. This may be accomplished by the

use of pituitary extract which has been shown to effect a great rise of systemic pressure and a decline of pulmonary pressure (Wiggers[6]).

In interpreting the changes of the heart sounds during this condition, it is necessary, however, to analyze more precisely the dynamic changes produced in the greater and lesser circulation in more detail.

(a) *The influence of pituitary extract on the greater and lesser circuits.*—Studies of the mean arterial pressures in the pulmonary and systemic circuits,[6] as well as the pressure curves in the right ventricle,[7] have led the writer to insist that the primary effect of pituitary extract on the heart muscle is a depressant one. It causes a decreased systolic discharge which, together with a slower rate, brings about a reduction in pulmonary arterial pressure. The effect on the right ventricular pressure is shown in segments A and B of Figure 10. The pressure

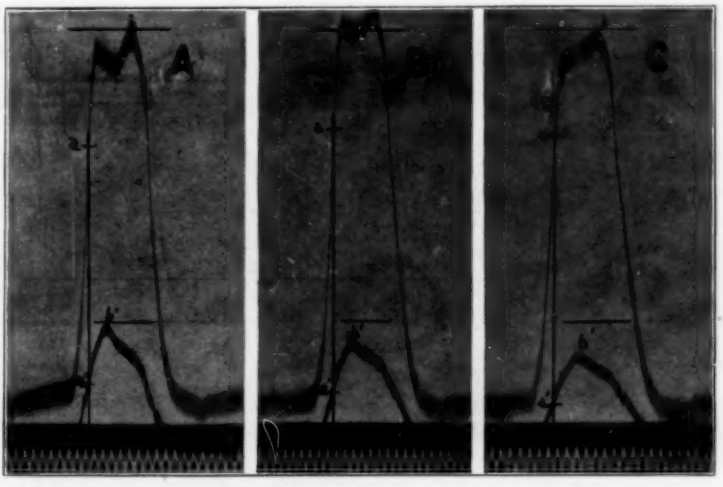

Fig. 10.—(One-half actual size.) Three segments of records showing left (upper curve) and right (middle curve) intraventricular pressure. A, before; B and C, during the stage of pituitrin action. Lower record = tuning fork vibration 0.02 sec. Detailed description in text. (Experiment C 206, XIII.)

during the end of the isometric period, as well as at the height of ejection, is evidently much lower. This is shown in the three segments of Figure 10 a′-b′). The effect on the left ventricle pressure is quite different. Owing to an intensive action on the musculature of the peripheral arterioles, the systemic pressure at once begins to rise. The left ventricle, thereby contracting against a progressively increasing

6. Wiggers, C. J.: Arch. Int. Med. **8**:30 (July) 1911.
7. Wiggers, C. J.: Am. J. Physiol. **33**:394 (Aug.) 1914.

tension, is forced to develop a considerably higher pressure during the isometric phase not only, but during the ejection period as well. This is shown on the three segments of Figure 10, at a and b, respectively.

The total effect of this extract therefore is to reduce the level to which the isometric and ejection pressures are raised in the right ventricle and to increase these levels in the left ventricle.

A study of the relative intensity of the heart sounds over different areas forms almost an experimentum crucis of our former conclusion, for if the intensity of the first sound depends primarily on the height of pressure during the isometric period of systole, and that of the second sound on the height of pressure at the beginning of diastole, then we should find that the intensity of the two pulmonary sounds, on

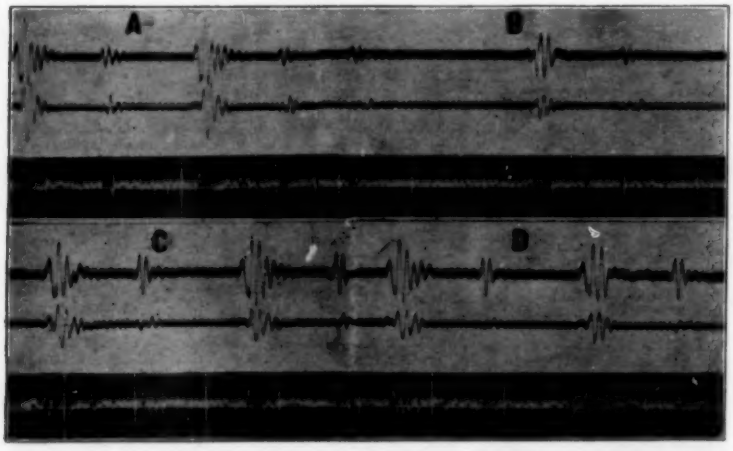

Fig. 11.—(Two-fifths actual size.) Four segments showing the amplitude of sounds. A, before; B, during slowing and first pressure increase following pituitary extract. C and D, subsequently—after marked elevation of pressure and return of cardiac rate to normal. Upper curve, apex sounds; middle curve, pulmonic sounds, lower curve, apex sounds. Time, abscissae, 0.04 sec. Detailed explanation in text. (Experiment C 143, V.)

the one hand, and the apex and aortic sounds on the other, would change in opposite directions during the action of pituitary extract.

(b) *The relative intensities of the heart sounds during the action of pituitary extract.*—Typical effects of pituitary extract on the two heart sounds are shown in Figure 11.

The changes in the first sounds may be considered first. During the rise of pressure (cf. segments A and B) the first sound decreases in all regions. This is, no doubt, due to a lowered isometric pressure

largely occasioned by the great slowing of the heart which complicates the action. The changes are similar to those produced by vagus slowing. As the arterial pressure rises to a maximum 1.2 while the isometric pressure elevates in the left ventricle and falls in the right (curves C and D), the first apical and aortic sounds increase in intensity while the second pulmonic sound decreases in intensity.

Comparison of the normal systemic and pulmonary sounds (segment A) with those occurring during the first cardiac slowing (B) shows that the second pulmonic sound is greatly reduced in intensity, and, in fact, may entirely disappear in some beats, while the second aortic sound is less affected. As the heart accelerates and the maximum pressure is reached within the systemic arteries (segments C and D) the second aortic and second apical sounds are markedly increased in intensity, agreeing with the previous dynamic analysis. The second pulmonic sound, on the other hand, continues to be of smaller amplitude as we should expect from the reduced pulmonary pressure.

VI. SUMMARY AND CONCLUSIONS

1. The heart sounds over the apex region, aortic and pulmonary areas were recorded simultaneously or in pairs by the direct sound recording capsules described by Dean and myself. Changes in the intensity of any heart sound over a particular area were determined by comparing the amplitude and number of vibrations entering into that sound complex before and after modified conditions of the circulation were experimentally produced.

2. The intensity of the first sound is not related to the volume of blood discharged by the ventricles, e. g., during slowing of the heart; when the systolic discharge is increased, the first sound is reduced in intensity.

3. The intensity of the first sound over all regions varies directly as the systolic tension developed within the ventricles — and there is good reason to believe, with the tension developed during the isometric period of systole.

4. The intensity of the second sound increases or decreases as the pressure (aortic or pulmonary) at the beginning of diastole.

5. When the pressures at the beginning and end of systole increase, particularly in one circuit and relatively little in the other, an accentuation occurs, predominantly in the sounds referred to the circuit in which the changes predominate.

6. In circulatory conditions where the pressures at the beginning and end of systole vary in opposite directions in the greater and lesser circuits, the intensity of the pulmonary and aortic sounds changes in opposite directions.

7. Direct experimental evidence supplements the anatomical basis for believing that sounds heard over the second left i. c. s. are transmitted from the right heart and lesser circuit, while those heard over the right second i. c. s. and apex have their origin in the left heart and greater circulation.

8. When reserve and caution are exercised, a change in the intensity of the first sound over any area is good evidence of a change in tension developed during systole of the ventricles, while a change in the intensity of the second sound over the aortic and pulmonary areas may safely be used as an index of a change of pressure at the beginning of diastole in the greater and lesser circuits, respectively.

PROLONGATION OF THE "S-T" INTERVAL OF THE VENTRICULAR COMPLEX AS SHOWN BY THE ELECTROCARDIOGRAPH *

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The study of electrocardiograms has advanced to a conspicuous degree the recognition of lesions of the heart. At the present time the interpretation of abnormal ventricular complexes is receiving considerable attention, and any observations which may bear on this question give sufficient excuse for their being recorded.

The normal ventricular complex has certain definite characteristics which, on the whole, fall within narrow limits. The main points, in which deviation from the normal may occur, are in the time occupied by the various parts of the ventricular complex and in the form of the deflections constituting this complex. For the sake of convenience the ventricular complex may be divided into two main segments, namely, the Q-R-S period and the S-T period. The Q-R-S period includes the primary deflections starting at the beginning of Q and finishing at the end of S. The S-T period commences at the end of S and terminates at the end of T. The sharp spike-like deflections of the Q-R-S period in the normal electrocardiagram are too well known to necessitate repeated description. The normal T deflection is less constant in its form, and as yet little is definitely known concerning deviations of this spike. The time relations of these two periods are definitelly known. In the normal electrocardiogram the Q-R-S period never exceeds 0.1 second, while the S-T period should not exceed 0.28 second. Thus the total Q-T interval in the normal electrocardiogram does not exceed 0.38 second. Although as yet the exact meaning of the T deflection is not definitely decided, it has been demonstrated that the termination of this wave coincides with the beginning of the second heart sound. Therefore it may be presumed that it represents the termination of the ventricular systole.

Animal experiments[1] have demonstrated that lesions of either the right or left branches of the bundle of His produce definite changes both in the form of the ventricular complex and in the duration of its

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* Read before the Thirty-Fourth Annual Meeting of the Association of American Physicians, June 17, 1919.

1. Eppinger and Rothburger: Ztschr. f. klin. med. **70**:1, 1910. Lewis and Rothschild: Phil. Trans. Roy. Soc., Series B. **206**:181.

various parts. Carter[2] has reported a series of cases showing changes in the ventricular complex analogous to those obtained by animal experiments and concludes that these are the result of lesions of one or other branches of the bundle of His. He lays down the principles that lesions of this character give the following changes in the ventricular complex.

(a) Q-R-S interval exceeds 0.1 second and, as a rule, constitutes more than one third of the entire complex.

(b) Relative increased amplitude of initial deflections.

(c) Final deflection T usually is in a direction opposite to that of the prominent initial deflection. May be upright or inverted.

(d) Initial deflections almost always show notching in one lead at least. Many bizarre forms are seen.

(e) Final deflection T frequently is much exaggerated.

These points form the basis for determining the gross lesions of the branches of the bundle of His. In a more recent communication the same writer[3] deals extensively with the pathological findings in such cases, not only in regard to the main branches of the bundle of His, but also in regard to the terminal arborizations. Oppenheimer and Rothschild[4] report a series of similar cases with fourteen necropsies, in thirteen of which there was present disseminated patchy sclerosis which was more marked in the left ventricle than in the right. Another important point brought out in their communication was the frequency of closure of the anterior descending branch of the coronary artery. This occurred in eight of the fourteen cases, and in four others there was pronounced diffuse coronary sclerosis.

Robinson[5] has reported a series of cases demonstrating various degrees of abnormal ventricular complexes under diverse conditions. Some of these cases show ventricular complexes which are practically identical with those of lesions of the branches of the bundle of His, while others are not so conspicuously aberrant. The same author has also drawn attention to the frequent temporary character of this condition, indicating that there is not necessarily a definite structural change present. That minor changes in the ventricular complex may indicate abnormal conditions in the ventricle has been demonstrated by Neuhof[6] in regard to the increased width of the R deflections, which sign he concludes is the result of myocardial degeneration.

2. Carter, E. P.: Arch. Int. Med. **13**:803 (May) 1914.
3. Carter, E. P.: Arch. Int. Med. **22**:331 (Sept.) 1918.
4. Oppenheimer, B. S., and Rothschild: J. A. M. A. **69**:429 (Aug. 11) 1917.
5. Robinson, G. C.: Arch. Int. Med. **18**:830 (Dec.) 1916.
6. Neuhof, S.: Arch. Int. Med. **22**:45 (July) 1918.

Up to the present attention has been chiefly directed to the prolongation of the Q-R-S period. But there is another abnormality of the ventricular complex which has received as yet little or no attention, namely, the prolongation of the S-T interval, and it is with this condition that the present communication is concerned chiefly.

TABLE 1.—Cases Manifesting Prolongation of S-T Interval without Prolongation of Q-R-S Deflections

Case No.	Elect. No.	Age	Cardiac Diagnosis	Transverse Dullness, Cm.	Pulse Rate	Systolic Blood Pressure	P.-R., Seconds	Q-R-S, Seconds	S-T, Seconds	Direction of T to Initial Wave	Preponderance Cornea
1	570	49	Hypertension	15	88	230	0.22	0.09	0.35	Same	Left
2	46	66	Myocarditis	13	96	190	0.16	0.10	0.32	Same	Left
3	112	58	Cardiorenal disease, anginal symptoms	20	100	180	0.20	0.10	0.32	Same	Left
4	307	15	Multiple endocarditis	16	86	120	0.20	0.08	0.34	Same	Left
5	288	58	Myocarditis, anginal	15	60	180	0.20	0.10	0.37	Same	Left
	316		symptoms		58		0.19	0.09	0.33	Same	Left
6*	317	69	Arteriosclerosis	18	68	140	0.19	0.08	0.31	Same	Left
7	156	40	Cardiorenal disease, anginal symptoms	16	67	210	0.21	0.09	0.32	Same	Left
8	332	67	Myocarditis, anginal symptoms	20	60	170	0.18	0.08	0.34	Same	Left
9	350	35	Mitral endocarditis, anginal symptoms	21	67	195	0.18	0.10	0.31	Same	Left
10	231	55	Myocarditis anginal symptoms	15	75	200	0.16	0.09	0.31	Same	Left
11	151	70	Myocarditis, anginal symptoms	12	54	160	0.20	0.09	0.35	Same	Left
12	110	63	Myocarditis, anginal symptoms	18	60	130	0.18	0.08	0.34	Same	Left
13	42	70	Myocarditis, anginal symptoms	19	75	210	0.18	0.08	0.38	Same	Left
14	328	50	Aortic disease, anginal symptoms	19	75	180	0.17	0.09	0.32	Same	Left
15	41	67	Aneurysm, anginal symptoms	13	65	140	0.20	0.08	0.32	Same	Left
16	312	60	Heart block	18	40	198	—	0.09	0.40	Same	Left
	312a		Myocarditis		43	195	0.2	0.09	0.40	Same	Left
17	4		Arteriosclerosis		43	180	0.4	0.16	0.54	Same	—
	19	70	Myocarditis	16	75	190	0.21	0.13	0.36	Same	—
	23				100	185	0.18	0.10	0.34	Same	—
18	550	77	Cardiorenal disease, anginal symptoms	20	75	185	0.12	0.09	0.35	Opposite	Left
19	506	38	Aortic valvular disease, anginal symptoms	21	70	140	0.18	0.09	0.32	Opposite	Left
20	409	54	Aortic valvular disease, anginal symptoms	23	86	154	0.16	0.09	0.32	Opposite	Left
21	477	47	Cardiorenal disease, anginal symptoms	24	70	230	0.20	0.10	0.32	Opposite	Left
22	395	58	Aneurysm	16	100	220	0.18	0.10	0.34	Opposite	—
23	561	71	Auricular fibrillation	21	75	200?	—	0.10	0.32	Opposite	Left
24	114	63	Auricular fibrillation, anginal symptoms	21	64	185?	—	0.09	0.32	Opposite	Left
25	394	45	Auricular fibrillation and heart block	17	31	120?	—	0.08	0.46	Opposite	Left
26	429	13	Multiple endocarditis	14	67	85	0.19	0.09	0.35	Same	Left

* Died of empyema.

PROLONGATION OF THE S-T INTERVAL

In Table 1 a number of cases are outlined which exhibit prolongation of the S-T interval without prolongation of the Q-R-S deflections. On analyzing these cases certain points of importance are evident.

1. *Transverse Cardiac Dulness.*—Although percussion is considered by some very competent observers to be a notoriously unreliable method of obtaining accurate data as to the size of the heart, it may be taken at least as a rough guide. In these cases the almost uniform enlargement of the cardiac dulness is most conspicuous. In only four cases is this measurement less than 15 cm. In one of these a child of 13 years of age (Case 26), a transverse cardiac dulness of 14 cm. is most abnormal, and it may be presumed in this case that there is distinct evidence that the heart was enlarged. In the other three cases percussion does not give conclusive proof of this condition. With these exceptions the physical examinations of all these patients would afford reason to believe that cardiac enlargement was the rule.

2. *Left-Sided Preponderance.*—The exhaustive work by Lewis and Cotton on cardiac hypertrophy and the electrocardiographic evidence of the relative preponderance of one side of the heart over the other, affords data for determining this condition. In these cases there was evidence of preponderance of the left side of the heart in all but two of the cases. In both of these the R spike was the principal initial deflection. Although the electrocardiographic evidence was wanting other considerations would lead one to suppose that cardiac hypertrophy did exist and to a conspicuous degree. The cases which do not show typical ventricular complex of left preponderance revealed, however, distinct enlargement of the cardiac dulness. On the other hand, the three instances in whom the cardiac dulness was not conspicuously increased there were typical ventricular complexes indicative of left preponderance. The almost uniform occurrence of electrographic signs of left preponderance coupled with the evidence of increase of the cardiac dulness affords strong presumptive evidence that cardiac hypertrophy existed in all these cases.

3. *Blood Pressure.*—Assuming that cardiac hypertrophy existed in these cases, it becomes necessary to account for such hypertrophy if possible. On investigating the systolic blood pressure[7] it is found that there is a pronounced elevation in eighteen of the twenty-six cases. In all of these cases there was evidence to indicate that this condition had existed for a considerable period. Furthermore, the cardiac diagnoses lend support to this view. All of these cases gave abundant evidence of chronic cardiovascular disease, although in many cases the signs were much greater than the symptoms would lead one to suppose.

7. The diastolic blood pressure was not always recorded, it has therefore been omitted; although it was uniformly increased in proportion to the systolic pressure.

In the majority of those cases with a normal or low systolic blood pressure other and sufficient reasons were usually present to account for the cardiac hypertrophy. Cases 14 and 26 were children with pronounced evidence of chronic rheumatic endocarditis. Case 6 was a patient suffering from a severe septic condition from which he eventually died. The history in this case was very suggestive of previous hypertension. In Cases 15, 19 and 20 there was evidence of extensive lesions of the aortic valves or the aorta, while in Cases 12 and 25 it was quite apparent that extensive myocardial changes had been occurring for many years. The evidence in favor of pronounced cardiac hypertrophy is almost uniformly present in these cases.

4. *Cardiac Rate.*—Slow cardiac rate is common in these cases. But the length of the S-T period is not constantly in proportion to the rate of the cardiac rhythm. There may be a progressive increase in the pulse rate with an associated diminution in the S-T interval until this reaches a more or less constant duration, and there may be a slight increase of the prolongation with slowing of the cardiac rate. But a variation in the length of the S-T interval without a proportionately conspicuous change in the rate of the cardiac rhythm occurs with fair frequency. Certain cases also show a parallel decrease in the P-R and Q-R-S intervals along with the decrease in the S-T intervals. This would lead one to suppose that this decrease was dependent upon an improvement in the function of the cardiac conduction system, which is comparable to the findings of Robinson in reference to the temporary character on occasion of Bundle Branch lesions.

Cases 5 and 17 (Table 1) also conform to this general improvement in conduction, which is also co-incident with an increase of the cardiac rate. On the other hand, in spite of an increase in the rate to normal, the S-T interval, and to a less extent the P-R and the Q-R-S intervals, do not completely return to the normal time limits.

Many of the cases recorded in Table 1 show a normal cardiac rate, but still there is a pronounced increase in the S-T interval as shown particularly in Cases 1, 8, 11, 12, 13, 18, 22 and 26. If the prolongation of the S-T interval were altogether due to slow cardiac rhythm it would be expected that after long diastolic periods the S-T interval would be greater than after short diastolic periods. This is found not to be so. In a case where there were diastolic periods of great length amounting to 20 seconds, the S-T interval of the ventricular complexes following such long diastolic periods averaged 0.56 second, while the S-T intervals during comparatively rapid periods of the heart's action averaged 0.55 second.

It is reasonable to suppose therefore that prolongation of the S-T interval is not altogether due to slow cardiac rhythm, although this may exert a certain influence.

CAUSE OF PROLONGATION OF THE S-T INTERVAL

The Q-R-S deflections are now accepted as being representative of the excitation wave passing through the main bundle of His, its main branches and their arborization. The work of Lewis and Rothschild has gone far to prove this theory. They bring forward evidence to prove that the length of time it takes for the excitation wave to appear on the surface of the heart depends upon two factors, namely, the length of the Purkinje tract, and the thickness of the ventricular wall. In the cases here reported it will be noted that the Q-R-S interval is either grossly prolonged, or is in the upper limits of normality, but yet the configuration of the ventricular complexes show little or no change from the normal, except in so far as the signs of left-sided preponderance are concerned. This prolongation of the Q-R-S interval in cases of left hypertrophy confirms a similar observation made by Lewis. This he attributed to the increased thickness of the left ventricular muscle. In certain cases this is not an adequate explanation, as the rapid changes in the length of this period could hardly be dependent upon like changes in the thickness of the ventricular.

Lewis makes the statement that "the length of the initial phases of the bigram may be taken to indicate the duration of the process of activation." Delay of this process of activation may be produced either by injury to one or other branches of bundle division, or by a generally lowered power of conductivity on the part of the conducting system as a whole.

The exact interpretation of the T deflection is not at present settled, but Lewis considers that it is indicative of the decline of the excitatory process. If this be the case, it would indicate that this is considerably retarded in the cases cited above. There is not enough evidence to hand at the present time to determine this question positively. However, the fact remains that there is a distinct prolongation of the ventricular systole which mainly occurs after the wave of activation has been completed. It would appear probable that this were due in part to the increased volume of the muscle, particularly as it has been shown that this has a distinct influence on the length of the activation wave as shown by the lengthening of the initial deflection.

It is well known that when a muscle is fatigued, the contraction time becomes distinctly slower. The heart in all these cases was laboring under a greatly increased burden and was performing the work in a comparatively satisfactory manner. It must be considered to what an extent the prolongation of the ventricular systole (S-T interval) is a compensatory phenomena the result of muscle fatigue.

The question of fatigue is associated so intimately with nutrition, that it was considered probable that some clue to the rôle played by muscle fatigue in producing prolongation of the S-T interval might be

found in cases of malnutrition. Such cases were not at hand, but it was observed that in cases of diabetes during periods of prolonged starvation, or during a very low calory diet, the S-T interval was distinctly delayed. It was found further, that when the diet was increased the S-T interval approached the normal, although it did not necessarily completely return within the normal limits (Table 2). Also it was observed repeatedly that on rest the prolongation of the S-T interval tended to diminish, although in other respects there was little or no change in the patients' condition except for a striking relief from the precordial distress.

TABLE 2.—EFFECT OF DIET ON S-T INTERVAL

Case No.	Elect. No.	Age	Diagnosis	Transverse Dulness, Cm.	Pulse Rate	Systolic Blood Pressure	P.-R., Seconds	Q-R-S, Seconds	S-T, Seconds	Direction of T to Initial Wave	Preponderance	Diet
1	268	28	Diabetes	11	73	99	0.18	0.06	0.39	Same	None	5 days starvation
	284				75		0.18	0.06	0.32	Same	None	Full diet
2	536	36	Diabetes	13	60	110	0.16	0.07	0.35	Same	Left	1 day starvation; 3 days 10 gm. H.
	555				64		0.16	0.07	0.30	Same		Full diet
3	550	29	Diabetes	..	83	115	0.16	0.08	0.32	Same	Left slight	Moderate diet, low fat
	552				88		0.16	0.08	0.28	Same	None	Full diet
4	540	26	Diabetes	12	70	118	0.17	0.08	0.32	Same	None	Moderate diet, low fat
	553				75		0.17	0.08	0.29	Same	None	Full diet
5	535	52	Diabetes	13	92	125	0.15	0.08	0.32	Same	Left	1 day starvation; 3 days 10 gm. C.H.
6	557	22	Diabetes	10	70	90	0.17	0.08	0.32	Same	None	1 day 64 gm.; 1 day 30 gm. C.H.
7	538	23	Diabetes	11	66	105	0.16	0.07	0.32	Same	None	Full diet; starved 3 days previously
8	573	67	Diabetes	13	83	120	0.16	0.06	0.30	Same	None	Moderate diet
9	576	5	Diabetes	9	75	80	0.16	0.06	0.29	Same	None	Low diet, no fats
10	577	60	Diabetes	13	72	70	0.13	0.09	0.32	Same	Left	Moderate diet

There were recorded in 65 per cent. of the cases, symptoms which for want of a better term have been classified as "anginal." These were usually characterized by precordial oppression or pain, sometimes radiating to the neck or the left arm. The acute paroxysms of "angina pectoris" were not frequent, although a history of such was sometimes obtained. There was described also a sensation of intense exhaustion. The question arises whether there be an association between the prolongation of the ventricular systole and these symptoms. It is an

accepted physiologic fact that the greater the resistance opposed to the contractile phase of muscular activity, the greater the degree of tension in the muscle. These symptoms usually occurred in cases with an increased systolic blood pressure, or in those showing conspicuous damage to the aortic valves or aorta. Under these circumstances the muscular load would be greatly increased, and as a result the muscular tension likewise. Cases which complain of intense paroxysms of precordial pain do not as a rule show lengthening of the S-T interval, which is suggestive that prolongation of the ventricular systole may be a beneficial phenomena in these cases, and that when it does not occur, cardiac spasm may result from increased work.

PROGNOSIS

The prognosis in these cases has been remarkably good in spite of a cardiac condition which frequently gave rise to considerable apprehension. As yet it has been impossible to complete statistics comparing the probable morbidity and mortality of these cases with similar ones without prolongation of the S-T intervals. The fact that none of these cases have died from cardiac failure, while many of them have been under observation for some years, leads one tentatively to consider this condition with favor.

CONCLUSION

1. Prolongation of the whole ventricular systole may occur without definite evidence of localized injury to the bundle of His or its branches.

2. Prolongation of the Q-R-S interval occurs with left-sided hypertrophy.

3. Prolongation of the S-T interval may occur with or without lengthening of the Q-R-S period, and is intimately associated with left-sided ventricular preponderance and precordial pain.

4. Similar prolongation of the S-T interval may occur in diabetes, particularly when the individual is on a very low calory diet.

PROGRESSIVE LENTICULAR DEGENERATION ASSOCIATED WITH CIRRHOSIS OF THE LIVER (WILSON'S DISEASE)*

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Our excuse for presenting before the association a case report with its postmortem findings is the rarity of the condition both in America and in Europe. Since Wilson first described the disease in 1912, not more than twenty-six cases have been reported, of which thirteen were observed by various American neurologists. The clinical history of our case was as follows:

REPORT OF CASE

H. B., white, male, aged 22 years, farmer by occupation, was referred by Dr. C. M. Wray of Iowa Falls, and admitted to the medical clinic, Dec. 11, 1916.

Entrance Complaints.—Painful cramps in the toes of the right foot and edema of both lower extremities.

Family History.—Father died at 45 years of age from tuberculosis of the lungs. Mother is alive and well. There are three brothers, two about patient's age and the third 5 years old, all living and well. One brother died in infancy. Two sisters, one 16 years old and the other 3 years of age, are living and well. The mother denies absolutely any similar trouble in her other children or other members of the family either on the maternal or paternal side. One great aunt died insane. There is no history of alcoholism, epilepsy, syphilis or other hereditary disease.

Personal History.—The patient was born and bred in Iowa and had all his life lived in that state or in Kansas or Minnesota. He was a farmer by occupation and of good habits. He used one cup of coffee a day, but no alcohol. He admitted chewing some tobacco and denied absolutely venereal disease. In childhood he had measles, mumps and whooping-cough, but denied scarlet fever, typhoid and rheumatic fevers. He was not subject to winter colds, bronchitis, pleurisy or pneumonia. He denied heart pain, palpitation and shortness of breath. Appetite and digestion were always good. For several years prior to his present illness he had been subject to attacks of diarrhea, lasting for two or three weeks, and usually assigned to some error in diet. The stools never contained blood or mucus. He denied absolutely having had jaundice, abdominal pain, nausea or vomiting. The urinary system was negative, except for slight nycturia. The patient denied headache, convulsions, nervousness or paralysis previous to the present illness. His brother stated that he had always been bright, intelligent and good natured, was popular with his friends and of average business ability. He had never appeared emotional and did not worry unnecessarily. The only accident that the patient recalled was an injury to the back of his neck five years previously, as the result of a kick from a horse; except that he was unconscious

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* From the Medical Clinic and Pathologic Laboratory of the University Hospital, State University of Iowa, Iowa City.

* Read before the Annual Meeting of the Association of American Physicians, May 1, 1917.

for about fifteen minutes there were no ill effects. For several years before the onset of his present trouble he had been bothered with cramps in the calves of the legs on first going to bed.

Present Illness.—Patient moved to northwestern Minnesota in June, 1916, where he worked on a farm for a Swedish family. His diet was of a general nature, except that meat was not often obtainable. About November 11, following several days of riding on a chain plow, he developed painful cramps in both feet, which were severe enough to cause him to give up his work and return home to Iowa, which he did about November 18. He had no difficulty in getting home by himself, but immediately on his arrival his family noted that he was quite emotional and had marked unsteadiness of his gait, as well as tremor of the hands and head, which gradually increased during his three weeks at home. He next noted gradual swelling of the shins, which was at first assigned to a bruise, the result of a kick from a horse while working on the farm in Minnesota. About Dec. 7, 1916, the family first noticed spasms of the hands, particularly when he grasped an object of which it seemed impossible to let go without assistance from some member of the family. On this account he was constantly watched so that he might be relieved of these painful spasms by relaxing the firm grasp of the patient; this procedure always resulted in immediate relief. Shortly after the swelling of the legs appeared there was also noticed some edema of the hands. There had been no fever, no difficulty with the bladder, no dysphagia and no dysarthria. At the onset of the illness the bowels were inclined to be loose, but recently had been quite constipated. The gait had become increasingly difficult and unsteady, so that he had to be accompanied to the hospital by his brother. His brother was certain that apart from his emotionalism his character was unaltered and that his memory and reasoning ability were good.

Physical Examination.—This was made December 12 by Dr. C. P. Howard. The patient is a sick-looking white male of stated age, with flushed cheeks, groaning with pain, which he refers to legs. This is at times apparently increased in severity, making him cry out for a few seconds. There is no characteristic tetanic position of the hands, which are held clinched and often holding the bedclothes. His arms are held almost straight. The thighs are semiflexed at the hips and the legs slightly flexed on the thighs, while the feet are extended to the full. There is no flexion of the toes on the feet. He grimaces a great deal and holds his breath for a few seconds during a paroxysm of pain. There is no Chvostek sign and no Trousseau sign. The upper eyelids are decidedly full and suggest edema. The lower lids are also a little puffy; the left hand seems a little puffy but does not pit on pressure. Both legs, but particularly the left, are edematous and pit on pressure. The skin of the lower leg is reddened and rough; over the left shin is an old scab about the size of a bean, which can be removed readily, leaving a granulating surface underneath; there is little or no infiltration. The skin everywhere is harsh and dry, suggesting that of ichthyosis. In addition there is a sudaminal rash over the chest and arms. The hair of the scalp, chest and arms is thin and fine; it is unusually scanty over the arms, trunk and legs; there are only a few axillary hairs and a sparse distribution of pubic hair, feminine in type.

The external genitalia are fairly well developed; the muscles are soft; the subcutaneous fat is about normal. The thyroid gland is palpable. The head is well shaped and rather small. The hands are not particularly large; the fingers are long and broad.

The chest is large and symmetrical. The lungs are clear throughout.

Heart: The apex beat is not seen but is just felt in the fifth interspace, 7 cm. from the midsternal line. The heart is not enlarged to percussion. The sounds are distant but regular and free from murmurs. The pulse rate is 76, regular, of good force and volume; the blood pressure is 110 mm. systolic and 60 mm. diastolic.

The abdomen is rather distended; the walls are held rigidly, but not board-like; when this rigidity is overcome deep pressure is permitted. Neither liver nor spleen can be felt.

There is no trismus nor risus sardonicus; no spasticity between attacks. The neck is freely movable, as are all the muscles at times. The tendon reflexes of both upper and lower extremities are normal. The abdominal reflexes are present. The plantar reflex is of the flexor type on both sides.

Blood Examination.—December 11. Hemoglobin, 110 per cent.; red blood cells, 4,410,000; white blood cells, 6,600; polymorphonuclear neutrophils, 62 per cent.; lymphocytes, 28 per cent.; eosinophils, 8 per cent.; transitionals, 2 per cent.

Blood culture taken and reported negative December 13.

The urine contained a slight trace of albumin, but was negative for sugar, acetone, diacetic acid and microscopically.

December 12. Blood: hemoglobin, 105 per cent.; white blood cells, 5,800. Polymorphonuclear neutrophils, 75 per cent.; lymphocytes, 21 per cent.; eosinophils, 3 per cent.; transitionals, 1 per cent.

In view of the possibility of tetanus, 5,000 units of serum were given intraspinously, 28,000 units intravenously and 8,000 subcutaneously at this time.

The coagulation time of blood was eight minutes and ten seconds (Brodie-Russel).

Cerebrospinal fluid: no cells; Noguchi globulin negative; no increased pressure. Wassermann reported negative December 16.

Serum Wassermann reported negative December 16.

Blood sugar, 0.45 per cent.; blood calcium, 13 mg. per 100 c.c. of blood.

The carbon dioxid content of the blood was 38 by the Van Slyke method and 27.9 volume per cent. by the Frederici method.

December 13. The boy seems more emotional today and thrashes about like a hysterical person. The mouth is dry. The throat is red, but with no exudate. The tongue is reddened. Edema of upper eyelids persists; that of the left hand has disappeared and that of lower extremities is markedly less, the left leg barely pitting on pressure and the right much less. The skin over the legs is reddened. There is resistance to passive motion of the right arm and leg, but none of the left arm and leg. On placing one's fingers into his right hand he gradually grasps them firmly and develops a tonic spasm of all the muscles of the extremities, which disappears when the grip is relieved. Trousseau's sign is absent after three or four minutes' pressure. Chvostek's sign is absent over the face and nerves of the upper and lower extremities. The tendon reflexes are not increased.

Dr. Beifeld reports that, owing to resistance of the patient, the electric irritability tests cannot be carried out with any degree of accuracy. He states, however, that it is not markedly increased.

December 14. The general condition is much improved. During our visit he was free from cramps. The edema of the extremities seems much less. The skin shows several linæ atrophicæ over the leg. The thyroid gland is just palpable and the trachea can be felt with great ease. Trousseau's sign was a little suggestive this morning.

December 15. The stool was brown in color and semisolid. Meyer's test for occult blood was definitely positive. Microscopic examination was negative.

The patient had a better night. He seems brighter. The edema has disappeared almost entirely even from the right leg. The eyelids are less puffy. He has had an occasional nosebleed. There is still some spasm of the lower extremities, with extension of the feet; there is also slight flexion of the fingers and wrists. On testing for the Trousseau sign the left hand assumes a curious position, more of a claw hammer than the obstetric hand and there are clonic movements of the fingers with apparently voluntary clonic movements of the arms. No Trousseau is present on the right side. No Chvostek sign is present on either side.

December 16. Dr. Beifeld reports that the electrical irritability is not increased.

Dr. L. W. Dean noted some exophthalmos, with von Graefe's sign. The fundi were negative.

Blood: white blood cells, 7,960; polymorphonuclear neutrophils, 68 per cent.; lymphocytes, 29 per cent.; eosinophils, 2 per cent.; transitionals, 1 per cent.

Following ingestion of 200 grams glucose no sugar appeared in the urine in four hours. The carbon dioxid of the blood (Frederici) was 30 volume per cent.

December 17. Last night was the best to date except for profuse sweating. The patient cries out every few minutes during the visit on account of painful cramps in legs. He denies pain in the arms. He claims that cramps are due to the grasping of things with the hands, which is an impulse hard to control. He frequently has periods of noisy breathing, but no periods of apnea. He eats fairly well; has no incontinence of urine or feces; continues to hold arms adducted with fingers flexed. The thumb is usually outside of the palm. The head is moderately retracted, usually turned to the right; no exophthalmus or any of the lid phenomena. The lips are slightly cyanotic. The cheeks are flushed. There is neither facial paralysis, spasm, tremor or Chvostek sign. There is more or less constant choreiform movement of the thighs. The legs are fully extended in talipes equinovarus position even in the absence of spasms. During painful spells the calves are distinctly contracted. The grips measured by the dynamometer are: right, 90; left, 40. He has difficulty in releasing the grip; he cannot elevate the arms above the head but keeps them in a constant swaying motion. The gross strength of the limbs appears normal. The tendon reflexes were all present except both Achilles reflexes which could not be elicited. Plantar and abdominal reflexes are normal. Sensation was intact throughout. The gait was interfered with by spasm of the calf muscles, which causes him to walk on his toes.

December 17. Hemoglobin, 88 per cent.; white blood cells, 14,080. Differential count. Polymorphonuclear neutrophils, 73 per cent.; lymphocytes, 23 per cent.; eosinophils, 4 per cent.

The urine showed a few red blood cells microscopically, but was otherwise negative.

The stomach tube was passed but no gastric content could be aspirated. On lavage the water returned without any solid material and was blood-stained, but the patient was bleeding a little from the nose and gums at times.

December 18. A second attempt for an analysis of a test breakfast was a failure, as the stomach was found to be empty at the end of forty minutes.

The patient was found bathed in sweat and presenting all the signs of a general infection, with slight tendency to cough and an occasional nosebleed. If anything the painful cramps have been more frequent recently. Examination reveals a dry, brown tongue. The heart was negative except for a soft, systolic murmur audible at the apex and over the precordia. The spleen could not be felt. There are still tonic spasms of the arms and legs which are now only painful in the hands. On attempting passive motion there is still definite resistance met with in all the muscle groups of the extremities. A second blood culture was taken today and reported negative on December 20.

The roentgenogram of the sella turcica showed no variation in size or contour from the normal.

December 20. The coagulation time of the blood by the Brodie-Russel method was six minutes.

A second lumbar puncture revealed no increase in pressure, six cells per c.c. and a negative Noguchi globulin test.

December 20. The patient developed incontinence of urine and stools and became very restless. He vomited on several occasions, and finally at 4 p. m. became comatose. One hour later, following a profuse dark emesis, he died.

The case was most obscure throughout its course. Tetany seemed excluded, though we thought of pluriglandular insufficiency and kept investigating along these lines. There was nothing to suggest an organic nerve lesion. He always appeared toxic and toward the end showed evidence of some terminal infection, with suggestive signs of a pneumonia. For three days before his death the temperature varied between 100 and 104 F.; the pulse ranged from 90 to 120 per minute and the respirations from 30 to 40 per minute.

The necropsy findings came as a great surprise. The cirrhosis of the liver was never even suspected. The liver itself was never palpable, and though the dulness was diminished this was assigned to the moderate tympanites present.

Necropsy.—December 21 (five hours postmortem), by Dr. C. E. Royce.

ANATOMIC DIAGNOSIS.—*Cystic degeneration of the basal ganglia; cirrhosis of the liver, colloid cystic degeneration of the parathyroid glands; bacteriemia; uniform congestion of the lungs.*

The body is that of an adult white male, about 5 feet and 11 inches in length, without deformity. The body is well nourished. Rigor mortis is well established. There is no edema present. The posterior surface of the body is livid. The face is also reddish purple in color, and rather blotchy in appearance. The same is true to a lesser degree of the upper part of the thorax. The skin over the elbows, about the umbilicus and over the left shin, is brown and rather scaly. There is a bloody discharge from the nose. On turning the body on the right side a considerable amount of bloody fluid runs from the nostrils. The superficial lymphatics are not enlarged. The pupils are round, regular and equal, measuring 3½ mm. in diameter.

On opening the body the abdominal cavity is found to contain about 350 c.c. of serous, slightly blood tinged fluid. The liver is seen to be very nodular. The omentum is thick, reddish yellow in color and rather dense. The peritoneal surfaces are nowhere adherent. The intestines are moderately distended with gas. The appendix is embedded posteriorly to the cecum. No fluid is found in the pleural cavities and there are no adhesions. The pericardial cavity contains 50 c.c. of clear yellowish fluid; no adhesions are present

Liver.—The liver is about the usual size and weighs 1,540 gm. and measures 24 by 18 by 8 cm.; its surface is very nodular, the nodules being nearly uniform in size, varying from 5 mm. to 1½ cm. and appearing evenly distributed on all the surfaces. The color of the nodules is a rather light grayish brown and the intervening tissue is brown. The cut surface shows that these nodules are evenly distributed through the substance of the liver and are of about the same size and number as were seen on the surface. The tissue of the nodules is rather friable; the intervening tissue is firm. There is no appearance of umbilication present.

Gallbladder.—The gallbladder is enlarged and distended. Its surface is a grayish white in color, and only by persistent and severe massage is it possible to express bile into the duodenum. The ducts are found to be patent and without deformity.

Spleen.—The spleen weighs 320 gm. and measures 13½ by 7½ by 4 cm. It is bluish in color and somewhat mottled, and the capsule appears wrinkled. It is bright red on the cut surface and its consistence is moderately firm.

Pancreas.—The pancreas weighs 190 gm. and measures 17 by 6 by 2 cm. and presents the usual lobulated appearance. It is grayish red in color and its consistence is uniformly firm throughout.

Esophagus.—The esophagus is regular in size and shape and has a smooth appearance on the inner surface.

Stomach.—The stomach contains about 50 c.c. of dark bluish fluid and the inner surface shows some erosions and areas of hyperemia.

Small Intestine.—Scattered through the small intestine may be seen patchy areas of bluish color. They measure about 2 by 2 cm., their general shape being square rather than round.

Large Intestine.—The large intestine presents on its proximal portion a general grayish-black discoloration of the mucosa, against which the lymphoid follicles appear as lighter colored substance, giving the appearance of trout skin.

Kidneys.—The kidneys are slightly larger than usual; the left kidney weighs 220 gm. and measures 12 by 7 by 4 cm., while the right kidney weighs 220 gm. and measures 11 by 7 by 4 cm. The surface of the kidney is smooth and regular. The capsule strips easily. The ratio of the medulla to cortex is as 1 to 2.5. The consistence is uniformly firm.

Suprarenals.—These glands are slightly enlarged. The left on section presents an excess of blood in the medulla; the right presents the usual yellow cortex and reddish-brown medulla.

Ureters.—The ureters are without deformities and are patent.

Bladder.—The bladder is smooth and without reddening.

Prostate.—The prostate seems slightly nodular, but is not enlarged.

Lungs.—The lungs are crepitant. They are both dark red throughout and exude a red, frothy fluid on section. Excised pieces float in water. Slightly lighter colored areas may be found scattered through the surface of the lungs, which on section are shown to be superficial. The left lung weighs 480 gm. and measures 22 by 14 by 9 cm.

Heart.—The heart weighs 290 gm. and was found filled with vermilion-colored liquid blood. The right border measures 10½ cm.; the left border 11 cm. The thickness of the left ventricle is 2 cm.; the thickness of the right ventricle is ⅛ cm. The muscle is firm, reddish brown in color and the valves are intact, and without deformity. The intima of the aorta and other blood vessels, as far as they were exposed, was reddish brown in color.

Thyroid Gland.—The thyroid gland was rather small, weighed 19 gm., was firm and smooth and in every respect appeared normal.

Parathyroids.—The parathyroids were readily found and presented no abnormality.

Testes.—The testes were both descended and to the naked eye appeared normal.

Brain.—The superficial portion of the brain shows an engorgement of all the blood vessels and a rather marked excess of cerebrospinal fluid. On manipulation of the brain a reddish fluid is seen to pour from the severed infundibulum. About 2 cm. of fluid was expressed in this way. The dura appeared normal except for discrete pea sized areas of opacity on its inner surface.

Pituitary Body.—The pituitary body is elongated transversely and weighs 920 mg. It is not especially reddened and its consistence is uniformly firm throughout.

The brain and the upper portion of the cervical cord were placed in formalin for five days and were then examined further.

The cerebrum divided horizontally by the Pierre Marie coupe d'élection shows in its lenticular nuclei a bilaterally symmetrical cavitation. The cavitation, however, is not sharply confined to the lenticular nucleus but involves, although to a lesser extent, the internal capsule and the optic thalamus. A few sharply circumscribed cavities are also seen in the white matter of the frontal lobes.

The cavities are sharply defined with smooth walls. The shape of each cavity is roughly oval or circular and the longest measurement of any one will not exceed 1 cm. There is slight grayish red discoloration of the globus pallidus. The putamen seems not to be discolored.

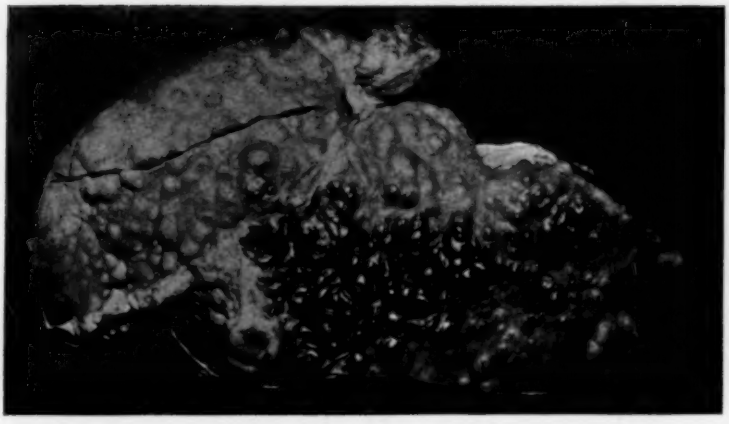

Fig. 1.—The liver.

Fig. 2.—Section of cerebrum showing the basal ganglia; a, caudate nucleus; b, putamen globus pallidus of lenticular nucleus; c, internal capsule; d, optic thalamus; e, lateral ventricle.

Otherwise the gross section of the brain presents nothing of comment. Neither in gross nor in microscopic preparations was there any pigmentation that would have suggested bile as its origin.

HISTOLOGIC DIAGNOSIS.—*Progressive degeneration of the neuron and glial elements of the basal ganglia, most extensive in the lenticular nucleus but involving the optic thalamus, caudate nucleus, internal capsule and red nucleus and to a slight extent the white matter just beneath the gray matter of the cortex.*

Chronic interstitial hepatitis; lymphoid hyperplasia manifest in spleen and retroperitoneal lymph nodes. Acute congestion of spleen and kidneys. Colloid cystic degeneration of the parathyroid glands.

HISTOLOGY: *Liver.*—The portions of the liver tissue which appear in the gross specimen as nodules projecting from the surface, on microscopic examination present an approximately normal histologic appearance. The intralobular tissue is thickened and infiltrated with leukocytes, many of which are of the polymorphonuclear type. The liver cells of these nodular areas present in some parts large numbers of fat spaces; in others greenish brown pigment granules may be seen. Congestion in these areas is not a marked feature. The tissue outside the nodules above referred to is composed of laminae separated by structures which look like bile ducts, and is everywhere infiltrated with red and white blood cells. Endothelial cells and fibroblasts are also numerous in these portions of the tissue. The leukocytes seen are largely of the small mononuclear variety.

Spleen.—The capsule of the spleen is thick and the trabeculae are broad. The finer reticulum of the spleen is increased in density. The pulp contains red blood corpuscles in large numbers. The malpighian corpuscles have their usual appearance and are somewhat overshadowed by large and denser lymphoid areas, in connection with which no blood vessels may be found.

Pancreas.—The tissue of the pancreas appears to be more compact than usual. With the higher powers the formation of the acini may be seen, but the cells are so crowded together that in most instances the lumen is not visible. The islands of Langerhans are also dense masses of tissue. In general, the nuclei are small with the cell body large.

A section from one of the large lymph nodes found near the pancreas shows hypertrophy of its constituent parts; the lymph follicles are increased in number. The endothelial linings of the lymph spaces are proliferated and the trabeculae are more dense than usual.

Kidney.—The kidney shows congestion and increase of connective tissue. The tubular epithelium is somewhat granular and the tubules are partly filled with granular débris.

Suprarenals.—The glands present their usual appearance, except that there is a little less regularity of arrangement among the cords. There is diminution in the size of the cells, so that their number appears greatly increased. The cytoplasm of the cells is dense, staining brightly with eosin.

Stomach.—The superficial portion of the mucosa is exfoliated. The epithelium of the tubules is in part missing and the remaining cells appear shrunken. The lymphoid nodules are numerous and dense. The sections from the small intestine show the same loss of epithelium.

Heart Muscle.—The cross striation is visible and presents marked irregularities in that the red and dark bands vary remarkably in their width at the thin portions of some fibers. The nuclei are swollen and present at their poles a few yellowish brown granules.

Lungs.—Most of the air sacs of the lungs are filled with red blood cells and with serum. There is no infiltration with leukocytes and the walls of the air sacs are not thickened.

Pituitary Gland.—The pituitary gland presents its usual glandular structure, without apparent alteration.

Thyroid Gland.—The usual histologic appearance of the gland is well preserved. The acini are dotted with desquamated epithelial cells in many instances.

Parathyroid.—The blood vessels are distended and engorged with red blood cells. The gland contains many acini, which are filled with colloid and present the same appearance as in the thyroid.

Testicle.—Sections from the testicle show the usual histologic structure without alteration.

Meninges.—Sections from the meninges at the site of the opacities in the gross preparation show simple fibrous thickening of the membrane.

Lenticular Nucleus.—Histologically, the lenticular nucleus differs from the normal in that the glial tissue is greatly rarefied, appearing as a loose meshwork which is varied in its structural size and density. The cells supported by this meshwork are the nerve cells found here in normal brains plus a few leukocytes, some of which are endothelial and some small mononuclear cells. The distribution of these leukocytes is indefinite. The blood vessels are thin walled, but contain large numbers of large rod shaped gram-positive spore bearing bacteria.[1] Weigert-Pal preparations of the lenticular nucleus show almost complete absence of myelinated structure in the affected portions.

Optic Thalamus.—A section through the optic thalamus including the border of a cavity shows the cavity to possess no definite lining. The wall, however, is smooth and regular. The tissue adjacent is rarefied by the presence of numerous small cavities which are elongated and tend to a concentric arrangement with the circumference of the large cavity. The nerve cells in this section appear not to be altered. In the walls of some of the blood vessels may be seen numbers of yellowish pigment granules.

Caudate Nucleus.—Histologic changes like those of the thalamus are noted, including the yellowish pigment in the walls of some of the vessels.

Internal Capsule.—Throughout the entire section imminent disintegration is apparent. Numbers of nerve cells remain intact but numbers are seen which are shadowy. Frequently about these cells the stroma has almost entirely disappeared. No pigmentation is seen in the walls of any of the vessels.

Red Nucleus.—Distinct cavities are found here and many more areas where the destruction of tissue has reached a point from which a cavity would have been formed. In these areas of partial destruction the characteristic is numbers of small cavities many of which open one into another and apparently by fusion of these large cavities are formed. Pigmentation is found in the walls of the vessels. As in other portions of the brain tissue where disintegration is in progress nerve cells with shadowy outlines may be seen.

Crus.—The sections show an accumulation of leukocytes within the blood vessels, but otherwise no irregularities. There is no loss of myelinated substance.

Pons.—The essential nerve structures and the supporting medium appear unaltered. The blood vessels are thin walled, but contain an undue proportion of leukocytes. Some are crowded by endothelial and polymorphonuclear leukocytes. Other vessels are surrounded by a scattering of small mononuclears. There appears to be no loss of myelin sheaths.

Medulla.—The medulla presents the same features as the pons.

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1. The presence of the above-mentioned bacilli together with gram-positive diplococci, also clumps and definite chains of cocci is demonstrable in all tissues examined.

Cord.—There are no histologic changes in the upper cervical region which was the only portion of the cord removed for examination.

Cortex Cerebri.—The cortex is intact in its essential nervous structure. The pia arachnoid is thickened and slighty infitrated with endothelial leukocytes and small mononuclear cells.

Cerebellum.—No changes are apparent in the cerebellum.

DISCUSSION OF THE CLINICAL AND POSTMORTEM FINDINGS

Even after leaving the necropsy room we were still completely at a loss for a diagnosis, and it was only after spending some time in looking over the literature that we stumbled across Wilson's[2] paper. It was then perfectly evident that we were dealing with a case similar to that described by Wilson and others. We, therefore, instituted a more careful examination of the brain after it had been hardened in liquor formaldehydi, and were gratified in finding the characteristic changes in the lenticular nuclei, as one can see clearly in Figure 2. The brain has been cut according to the Pierre Marie coupe d'élection method. This reveals a bilateral symmetrical cavitation and atrophy of the lenticular nuclei. As you will see even with the naked eye the cavitation is not sharply confined to the lenticular nucleus itself, but involves, although to a lesser degree, the internal capsule and optic thalamus on both sides. There is a slight grayish discoloration of the globus pallidus.

Anyone conversant with Wilson's paper will immediately recognize the strong similarity to those described as acute cases of lenticular degeneration. So far as can be determined by the history of our case, it ran a shorter course than any heretofore reported. So far as the clinical symptoms are concerned, there is little to note as peculiar from the other cases. Mentally, he was distinctly emotional, but otherwise normal. The peculiar choreiform movement of the extremities, the muscular rigidity and hypertonicity, the painful spasmodic contractions, have all been noted in the cases reported by others. Our case possibly showed more than usual the phenomenon of perseveration, by which we mean a tendency to grasp spasmodically various objects, as the bedclothes, back of a chair and the hands of the examiner, resulting in a painful spasm until disengaged by the nurse or attendant. We were interested in finding this mentioned by Mills,[3] but with this exception, it had not been noted in any other patient but our own. The vasomotor phenomena of redness and edema of the skin were also exceptional, and have only been noted previously by Mills. The examination of the reflexes, both superficial and deep, and of the various forms of sensation, as well as the special senses, was as usual

2. Wilson, S. A. K.: Brain **34**: Part 4, 1912.
3. Mills, C. K.: Neurol. Centralbl. **33**:1266, 1914.

entirely negative. While no special tests were made of the hepatic function, none of the usual signs of hepatic insufficiency were manifest. Wilson and all the other writers constantly confess that even when from their former experience they were on the *qui vive* for signs of cirrhosis of the liver, these were conspicuous by their absence during life. Only in an occasional case has the liver been noted as palpable or decreased on percussion. Very rarely has jaundice been noted.

As regards the postmortem findings, nothing could be more typical than our case, with the exception that the lesion was not absolutely confined to the lenticular nucleus. Wilson, in his original description, is inclined to emphasize the limitation of the process to the putamen and globus pallidus of the lenticular nucleus and to the caudate nucleus, but as one would naturally suppose additional case reports have shown that the process is not always restricted to the lenticular and caudate nuclei. Ours is not the first in which the optic thalamus, and even the internal capsule and motor cortex, have been involved. In others the pyramidal tracts of the spinal cord have shown slight degeneration. Our case, therefore, may be grouped with several others in which, though the brunt of the process has been borne by the basal ganglia, other portions of the nervous system have been affected. As regards the cirrhosis of the liver, there is considerable dispute as to whether it is a true cirrhosis or some other form of degeneration, but most are agreed with Wilson that it must be classified as multilobular or mixed cirrhosis.

Any student of neurology will be struck with the close resemblance between the clinical phenomena of Wilson's disease and that of pseudosclerosis as originally described by Wesphal[4] and Strümpell.[5] In fact, many are forced to confess that it is impossible to distinguish between the two diseases until a complete macroscopic and microscopic study of the brain and other portions of the nervous system have been made. In reading over the numerous cases described as pseudosclerosis, one is struck rather by the comparative lack of complete examination of the brain and cord than by the absence of definite pathology in the completely examined cases. In fact, I must agree with various recent writers on this subject, who state that the difference between the two diseases seems to be an anatomical one; that is to say, in pseudosclerosis the process is more widespread; in a pure Wilson case more localized. The involvement of the cortex accounts no doubt for the greater alterations in mentality in pseudosclerosis than in the other condition. But as our case illustrates there appear to be all degrees

4. Westphal, C.: Arch. f. Psychiat. **14**:87, 1883.
5. Struempell, A.: Deutsch. Ztschr. f. Nervenheil. **12**:115, 1898; **14**:398, 1899.

in the extent of the process from that confined entirely to a portion of the lenticular nucleus to a most widespread degeneration of the central nervous system.

We do not wish to be understood to belittle in any way the accuracy and sharpness of the clinical picture drawn by Wilson, being merely anxious to note the self-evident truth that there is no morbid process, however apparently specific and selective, which restricts itself in its production of clinical and pathological phenomena.

As to the pathogenesis, much has been written. Wilson believes that the degeneration of the lenticular nucleus is due to the selective action of some morbid agent on its cells and fibers and found that this morbid agent was in all probability a toxin associated with a hepatic cirrhosis and possibly generated in connection therewith. He drew the important analogy of the occurrence of so-called "Kernikterus" in certain cases of familial icterus gravis neonatorum, "where in spite of the universal bile-staining of the tissues of the body certain collections only of gray matter in the brain show a marked affinity for the circulating poison while others do not." "The parts that are stained deeply are in particular the nucleus lenticularis and the corpus Luysii (among others), while the optic thalamus, for instance, is scarcely stained at all."

What interested me especially in the literature of pseudosclerosis was a small series of cases[6] which presented among other phenomena an annular yellow pigmentation of the cornea in addition to the cirrhosis of the liver and changes in the nervous system. Further, in three cases either diabetes mellitus or glycosuria or a lowered carbohydrate tolerance was noted. The pigment was thought by some to be silver, by others manganese, while one or two have suggested its close resemblance to that pigment seen in hemochromatosis. We would suggest, therefore, that in the future study of all cases of cirrhosis, and particularly of those associated with marked pigmentation as is true in hemochromatosis, a more careful examination should be made of the basal ganglia in particular and of the nervous system in general.

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6. Kayser, B.: Klin. Monatsbl. f. Augenheilk. **40**:22, 1902. Anton, G., and Meyer, O.: Virchows Arch. f. path. anat. **201**:349, 1910. Salus, R., and Westphal, A.: Arch. f. Psychiat. **41**:1, 1913. Fleischer, B.: Klin. Monatsbl. f. Augenheilk. **41**:489, 1903. Kubitz, A., and Staemmler, M.: Beitr. z. path. Anat. u. z. allg. Path. **60**:76, 1915.

THE ENERGY INDEX (S. D. R. INDEX) OF THE CIRCULATORY SYSTEM

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Of all that has been said pertaining to the measurable functions of the circulatory system, there are three well-established facts: they are the systolic pressure, the diastolic pressure and the pulse rate. Very much more than this has been proposed by various investigators, but the fact remains that none have met with universal approval.

In this communication I propose the S. D. R.[1] index which is based on these three known factors. The point of systolic pressure represents the culmination of force inaugurated by the systole of the heart. The point of diastolic pressure represents the highest level of sustained pressure during the diastole of the heart. Each pulse beat consists of a systole and diastole. Irrespective of the length of time occupied by the systole and diastole, together they represent the total effort of a single pulse beat. Figure 1 is a graphic representation of six pulse beats.

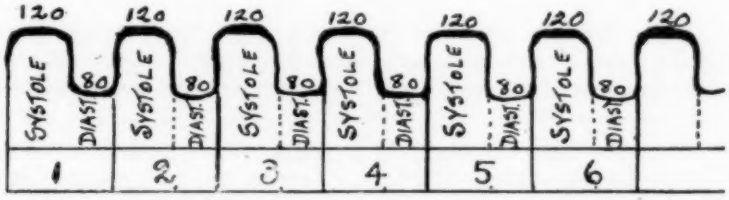

Fig. 1.—Graphic representation of six pulse beats, each beat consisting of a force of 200 mm. Hg.

For example, if in a given case the lifting force of the systole is 120 mm. Hg and the diastolic force is equal to 80 mm. Hg, then the force of the pulse beat which comprises both phases is 200 mm. Hg. This, multiplied by the number of beats, indicates the total force per minute. It should be noted that I use the term "indicates," and not "measures," which may be applied to absolute values.

Now, why this calculation? Simply because neither the pulse rate nor the systolic pressure nor the diastolic pressure taken alone gives us sufficient information. Each element of the triad is constantly changing and adjusting itself to the others — and it is the concerted action of the three forces which maintains the circulatory equilibrium. As

1. Barach, Joseph H.: The Energy Index, J. A. M. A. **72**:525 (Feb. 14) 1914. The Energy Index of the Circulatory System, Am. J. M. Sc. **152**:84 (July) 1916.

is well known, a high systolic pressure is compensated largely by a slowing of the pulse rate. A low diastolic pressure is compensated by an increased pulse rate, and so on. Like the triangle of limited area, alteration in the length of one leg of the triangle results in a change of the other two.

Effect of Gravity on the S. D. R. Index.—To illustrate the point, let us take a simple example. Table 1 is based on observations made on forty-eight normal adults. The subjects were placed on a table with a movable top. The first observations of blood pressure and pulse rate were made with the subject in the erect posture. Then the table top was tilted to the horizontal and the second observation was made. After this the table top was again placed in the perpendicular and the third observation was made. The results were as follows:

TABLE 1.—OBSERVATIONS OF RELATION OF POSTURE TO PULSE AND BLOOD PRESSURES

	Erect	Horizontal	Erect
Pulse	×	—	+
Maximum Blood Pressure	×	+	—
Minimum Blood Pressure	×	—	+
Pulse Pressure	×	+	—
Venous Presure	×	—	+

This illustrates the adaptation of the three factors which occurs as a result of a mere change in the body posture, with all voluntary effort eliminated. It is the effect of gravity on the function of the circulatory system.

Effect of Effort on the S. D. R. Index.—Table 2 shows the effect of graded effort on the S. P., D. P. and P. R. Eighty-two healthy young men did a complete squat at the rate of from thirty-three to fifty times per minute, with the following results:

TABLE 2.—EFFECT OF SQUATTING ON BLOOD PRESSURE AND PULSE RATE

	S.P.	D.P.	P.R.
20 squats at the rate of 33 per minute resulted in	+	—	+
20 squats at the rate of 36 per minute resulted in	+	—	+
20 squats at the rate of 44 per minute resulted in	+	+	+
20 squats at the rate of 46 per minute resulted in	+	+	+
20 squats at the rate of 50 per minute resulted in	+	—	+

The increase or decrease of each of the values is plainly seen. Needless to say, the S. D. R. index showed the effects of the exertion in proportion to the work done and condition of the individual.

Reaction to Epinephrin; the Test of Goetsch.—Here the individual, after resting quietly in the horizontal position for half an hour, is given an injection of 0.5 c.c. epinephrin solution, 1:1,000. Depending on

sensitiveness to epinephrin, we produce a certain effect on the circulation, more marked in some than in others. The following two examples illustrate the point:

TABLE 3.—EFFECT OF EPINEPHRIN ON CIRCULATION

Negative Case			Positive Case		
Before Epinephrin	Height of Reaction	After	Before Epinephrin	Height of Reaction	After
S. ..... 125 mm. Hg.	136	117	S. 108	140	108
D. ..... 80 mm. Hg.	82	70	D. 70	70	65
R. ..... 94 per minute	90	80	R. 84	112	84
Index 19,270	Index 19,620	Index 15,160	Index 19,852	Index 23,520	Index 14,532

To offer many more examples of the application of the S. D. R. index is unnecessary. Whenever a change occurs in the activity of the circulatory system, the S. D. R. index will show the change. The S. D. R. index indicates the degree of activity of the circulatory system. It is not intended to measure the work of the heart, although it indicates that better than some of the formulas proposed for that purpose. It does not help us to distinguish the cardiac load from overload, nor cardiac strength from cardiac weakness, nor velocity. What may be said for the index is, that it indicates the amount of energy expended by the circulatory system in the performance of its function, and that it gives us information which we do not get from any one or two elements in the triad.

The Normal Index.—In a previous communication based on observations made on 250 normal young men, I designated the upper limit of a normal index as being 20,000 mm. Hg pressure per minute. This was true of young men from 18 to 30 years of age in civil life. If, as we did in the Army, we take large numbers of older men, and include men who, although not perfectly normal according to medical standards, yet were acceptable for military service, we would find that a considerable number would show an index between 20,000 and 25,000. But this group will be made up largely of cases of tachycardia, moderate hypertension and simple cardiac hypertrophy.

The Energy Index as Found in the Cardiovascular Examination of the Army.—The figures to be quoted here were obtained from duplicate records made after the examinations were finished and the men had been accepted or rejected. Of the 26,396 men examined in one period of forty-seven days, 1,171 questionable cases were picked out for special examination by our cardiovascular board. This examination was made according to the form B. 1. This examination included the history of the subject, the accurate measurement of the heart, recording of any arrhythmias, the character of sounds and murmurs, taking of blood pressure and the complete exercise test, i. e., pulse in the erect and in the horizontal position, hopping 100 times, taking pulse

immediately after exercise, and two minutes later while the subject is still in the horizontal position. The 1,171 cases constitute all but the apparently perfectly normal ones of the series, including all cases which showed disturbances of rhythm, any abnormal sounds, prominent apex beats, abnormal pulsations, dyspnea, etc. Of these 1,171 men, 996 were finally accepted and 175 were rejected. Of the 175 rejects, 138, or 78 per cent., had an index of not more than 20,000. In other words, if our entire cardiovascular examination consisted only of determining the S. D. R. index, and this compared to the most complete and thorough examination according to the standard of the U. S. Army, we would have been correct in 78 per cent. and incorrect in 22 per cent. of the questionable cases. When we compare the errors into which the S. D. R. index would have led us in the entire series of 26,396 cases, we find the remarkably small figure of 0.05 per cent. This illustrates the value of the S. D. R. index.

TABLE 4.—CASES REFERRED TO THE CARDIOVASCULAR BOARD

	Per Cent.
Tachycardia, simple	30.0
Normals	26.0
Murmurs without significance	9.0
Combined lesions	6.0
Hypertrophy with hypertension	5.0
Hypertrophy without hypertension	5.0
Mitral insufficiency	3.0
N. C. A.	3.0
Sinus arrhythmia	2.6
Extrasystolic arrhythmia	2.4
Myocarditis	2.0
Mitral stenosis	2.0
Aortic insufficiency	2.0
Hyperthyroidism	2.0
	100.0

Needless to say, the abnormalities in our men were similar to those reported by other cardiovascular examining boards, as Table 4 shows. Furthermore, in searching for the type of case in which the greatest error occurs when the S. D. R. index is used as a guide, I find that in the 22 per cent. of the cases which were accepted by us, and which would have been rejected on the basis of the S. D. R. index, more than three fourths of them were tachycardias. Now, every one who has had to decide as to whether to accept or reject a case of tachycardia, knows how perplexing a problem it is. Probably we erred more frequently in accepting than in rejecting this type of case, expecting that if the man could not perform the duties of a soldier—he would be reclassified later—rather than reject a man who in a few days after the first rush of duties would perhaps return to normal, we accepted him. Later experience showed us that the men with tachycardia whom we accepted were the very ones that showed cardiac insufficiency when they began to experience the hardships of military training.

DISCUSSION AND CONCLUSIONS

1. The S. D. R. index based on the three known factors of the circulation indicates the state of activity of the circulatory system.

2. Normally, the index is found to be about 20,000 mm. Hg pressure per minute.

3. The index does not indicate "heart disease" or "decompensation" or physical fitness. It designates the amount of effort which the circulatory system is putting forth at the time.

4. A high index means increased cardiovascular effort, either the action of the heart and blood vessels is accelerated because of inability to accomplish their work at a normal rate of activity, or they are fully capable of doing their work, but the resistance to their functionating is great. Either condition is pathologic, and the variation of the index from the normal calls attention to this.

5. A low index means either that the circulation is accomplished with little effort or an inability to expend the necessary effort.

6. Minor changes in the circulation, such as are produced by the slightest alteration in the bodily functions, the effect of drugs, etc., may be detected by the S. D. R. index.

7. The S. D. R. index as a guide to abnormalities in function of the cardiovascular system in a series of 26,396 was correct in 99.95 per cent. In cases referred for special cardiovascular examination, i. e., in the clinically doubtful case, the S. D. R. index proved a correct guide in 78 per cent.

Of the 22 per cent. in which the index failed us, more than three fourths of the cases were tachycardias, and it cannot be said positively that the index was wrong.

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MENINGOCOCCUS MENINGITIS AT CAMP LEE

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The epidemics of meningococcus meningitis occurring in a number of the army camps have afforded an unusual opportunity for the study of the disease. There have been numerous reports in the literature for the past year emphasizing various phases of the infection.

The disease had previously been studied so thoroughly and carefully by Flexner and his associates at the Rockefeller Institute that the experiences of most observers during the army epidemics have only confirmed previous findings. It seems that the one outstanding contribution to the study of the disease during the past two years is the conception of the infection as primarily a generalized one with a secondary localization in the meninges. For this view we are indebted largely to the work of Herrick[1] and his associates at Camp Jackson where many cases of meningitis have been studied. Workers at other camps have not been unanimous in accepting this view, but Herrick's work has been confirmed in other base hospitals, notably at Camp Beauregard by Landry and Hamley,[2] who subscribe fully to his views. Of course it had long been known that there was a type of the disease fulminating in character in which the infection was evidently generalized. But it had been held that the majority of cases were primarily a localized infection from the outset.

A necessary corollary of the conception of the disease as a generalized infection has been new ideas in regard to treatment. It has been shown that intravenous therapy influences markedly the course and outcome of the disease. This result is well illustrated in the Camp Jackson series of 265 cases. Of 137 patients receiving intraspinous treatment alone 34.3 per cent. died; in 128 cases with combined intraspinous and intravenous therapy the mortality was 14.8 per cent. The point is emphasized also that it is the severe cases in which the newer methods of treatment are most effectual. Mild cases of the disease respond readily to almost any treatment, even spinal drainage alone. It is for the severe cases that we have most needed improved methods of treatment.

Intravenous therapy also decreases the number of intraspinal treatments needed. It has seemed to us that the harm resulting from con-

1. Herrick, W. W.: Arch. Int. Med. **21**:541 (April) 1918; J. A. M. A. **71**:611 (Aug. 24) 1918.
2. Landry and Hamley: Am. J. Med. Sc. **157**:216 (Feb.) 1919.

tinued intraspinal treatments has not been emphasized enough. The majority of the bad effects of the disease are due to a myelitis in the caudal region and involvement of the nerve roots. This is the direct result of the local introduction of serum and needle traumatism, and is the explanation of the pain and stiffness of back and legs so often complained of. Rosanoff[3] from the study of twenty-six convalescent cases has described what he considers a uniform postmeningitic syndrome. One can see that the most of the symptoms are directly dependent on changes in the spinal cord and nerve roots at the site of the local treatments.

At Camp Lee we have fortunately not had to deal with any large epidemic of meningitis, but cases have developed from time to time, usually in groups. From June 1, 1918, to June 1, 1919, thirty-one patients have been treated in the base hospital.

We have been interested in the analysis of the cases especially from the standpoint of the evidence they present for or against the disease being primarily a generalized infection, and also the results of treatment.

The cases have been quite generally distributed throughout the year and throughout the camp so the epidemic factor has played only a small part. The distribution by months has been as follows: June, 1918, one; July, 1918, one; September, 1918, four; October, 1918, eight; November, 1918, four; December, 1918, nine; January, 1919, three, and February, 1919, one. Every case came from a different company.

Twenty-one of the thirty-one patients, or 67.7 per cent., showed unmistakable evidence of a generalized infection before there were any signs of a localization in the meninges. Fourteen had petechiae, usually in large numbers; one had a macular rash; in thirteen records there is no mention of a rash, and in two cases it was absent. In six cases in which there was no rash the only symptoms for a period varying from seven to twenty-three days were the signs of a generalized infection, viz.: fever, general malaise, joint pains and enlarged spleen, usually with an upper respiratory tract infection of varying degree. The evidence of meningitis did not develop until late, and when lumbar puncture was done there was usually only a small number of cells in the spinal fluid. The meningitis as evidenced by the cellular reaction in the spinal fluid was only of a minor degree as compared with general infection. This type of case has been emphasized by Herrick in a recent paper.[4] The following case illustrates the type as we have observed it here. The generalized infection overshadows the

3. Rosanoff, A. J.: J. A. M. A. **71**:1476 (Nov. 3) 1918.
4. Herrick, W. W.: Arch. Int. Med. **23**:409 (April) 1919.

local picture. Unfortunately, this patient was treated during the period in which only intraspinous and subcutaneous therapy was being used. The response to treatment was very slow.

CASE 1.—Patient aged 23 years, white, was admitted to the hospital Oct. 16, 1918. His family history was unimportant, and his personal history was negative, except that he had been treated in the base hospital from September 24 to October 4 for influenza and bronchopneumonia. He stated that he had begun to feel badly the night before admission, but had gone to work the next morning. He complained of headache, fever, chilliness, anorexia, pain in joints and backache. The general examination was negative, except that it was noted that he was nervous and irritable. His temperature was 103.2 F., pulse 120, and respiration 24. His temperature was normal for the next three days followed by an irregular temperature for forty-eight hours. October 26 he had a chill with a sharp rise in temperature, and October 29 there was again an unexplained fever of 103 F. Examination was negative, except for a palpable spleen. After several days of normal temperature he was discharged to quarters without satisfactory explanation for his symptoms. November 6 he had headache, general achiness, chilliness and slight vague abdominal symptoms and he was returned to the hospital with a diagnosis of acute rheumatic fever. His temperature was 100 F. The examination was negative, except for tenderness in the right iliac fossa. The next day he had headache and vomiting and twenty-four hours later there was slight neck rigidity, the white blood cells numbered 24,400 and the temperature was 103 F. The Brudzinski sign was negative and the Kernig was only suggestive on one side. Lumbar puncture showed cloudy fluid. The cell count of the fluid from the first puncture is not recorded, but the fluid on the following day showed only 1,018 cells per c.c. He was given 260 c.c. of antimeningococcus serum intraspinally and 475 c.c. subcutaneously. Thirteen lumbar punctures were made. He was sent to the Development Battalion for further hardening, Dec. 19, 1918.

The analysis of the results of treatment in our series is interesting. The cases are divided almost equally into two groups. In the first group, which covers the period from Sept. 15, 1918, to Dec. 7, 1918, intraspinous and subcutaneous treatments were used in twelve cases. Four patients received intraspinous treatment only. We discount entirely the value of the serum given subcutaneously. The mortality in this group was six deaths, or 37.5 per cent.

The second group comprises fifteen cases treated in June and July, 1918, and during the period from Dec. 7, 1918, to March 1, 1919. Eleven patients in this group received both intraspinous and intravenous therapy. Four cases of the mild type, one of which was transferred late in the course of the disease from another camp, were given only intraspinal treatment and recovered promptly. Only one patient of the fifteen died, a mortality of 6.6 per cent. This patient died within thirty-six hours after admission to the hospital.

I realize that no sweeping deductions can be drawn from such a small series, but one in daily contact with the patients could not but be impressed with the good resulting from the intravenous administration of serum. In the second group of cases the patients were on the

average much sicker than those in the first group, and a study of the clinical records convinces us that some of the patients receiving only intraspinous therapy could have been saved by serum given intravenously. In one case reported elsewhere I believe the intravenous injection of glucose was probably the factor determining the outcome of the infection. The value of glucose in reducing the brain volume has been emphasized elsewhere.[5] We believe it is a valuable adjunct as a routine measure in meningitis.

The view is held by some, notably by Neal,[6] that the only value of serum given intravenously is to destroy bacteria circulating in the blood stream. But there must be a passage of antibodies from the blood stream into the spinal fluid through the choroid plexus, and also into the tissues of the central nervous system. And it is really the tissues that are the seat of infection, and not the spinal fluid.

The following case is cited to show the evident effect of serum given intravenously on the affected tissues of the central nervous system and also presumably on the spinal fluid.

Case 2.—Patient, white, aged 36 years, was admitted to the hospital May 31, 1918, with an evident cerebrospinal meningitis. There was a profuse crop of petechiae and he was very ill. The second day he had an arthritis affecting the left wrist. He at first improved under intraspinous treatment. June 4 he became worse, the spinal fluid was more cloudy and meningococci reappeared. Intravenous injection was attempted but stopped after only a few c.c. had been given because he did not react well. He again became worse on the ninth but then improved and became afebrile. June 27 he began to have fever, headache and vomiting and lumbar puncture showed turbid fluid. After three intraspinous treatments his temperature returned to normal. July 6 he began to have an irregular rise in temperature. He complained of headache but there was no stiffness of the neck or vomiting. On attempting intraspinal treatment again it was found that the spinal fluid had become so thick that it would not run out. Only a few drops could be obtained at each puncture even by aspiration. The introduction of serum had to be abandoned. Meningococci were present in the fluid obtained July 16. Up to this time 440 c.c. of serum had been given in twenty-eight punctures. At this time intraspinal treatment was given up and 435 c.c. of serum given over a course of six days in seven intravenous injections. After each injection there was a reaction with chill and fever. His temperature remained normal after the last treatment. He had a partial paraplegia evidently from caudal and nerve root involvement subsequent to the many intraspinal treatments and was deaf. He was transferred to a general hospital, Oct. 20, 1918, for further convalescence.

The infection in this case which seemed to be localized in the central nervous system was cured by serum given intravenously. A similar case is reported by Camac.[7]

5. Haden, R. L.: To be published in J. A. M. A.
6. Neal, Josephine B.: J. A. M. A. **72**:1785 (June 14) 1919.
7. Camac, C. N. B., and Bowman, Karl M.: Arch. Int. Med. **23**:17 (Jan.) 1919.

I believe that there is a tendency to overemphasize the danger of the intravenous administration of serum. This is certainly not to be undertaken inadvisably, but in competent hands should be perfectly safe. We have used routinely 100 c.c. at each injection, giving it at intervals of twelve hours for the first three to five doses. The intraspinal treatments have been given twice daily. One of the most fundamental points in the serum therapy is to give it in large doses, the optimum being 100 c.c.

I have been very much impressed by local ill effects of intraspinal therapy. In every case in this series in which a large number of punctures were employed there has been evidence of a caudal myelitis and nerve root injury leaving what bid fair to be permanent residuals. In no case in which intravenous therapy was instituted early has this occurred because much fewer intraspinal treatments were necessary. It has been common to have develop also in those patients receiving many treatments by spinal puncture delirium, increased rigidity, headache and fever for a period of several days. This usually came on well after the period of serum sickness. Dopter[8] ascribes the condition to the mechanical and toxic effects of the reaction leading to the formation of precipitin in the spinal fluid.

The complications in the recovered cases have been as follows: Panophthalmitis, one case; deafness and partial paraplegia, one case; paralysis of sixth cranial nerve and of musculospiral nerve, one case; arthritis (excluding serum arthritis), three cases, and arthritis and paralysis of sixth cranial nerve, one case.

I cannot emphasize too strongly that each case of meningitis must be studied by itself, and all the factors in the case taken into consideration before the plan of treatment is determined. While I believe that every case of meningitis is primarily a blood stream infection when the case is first seen by the clinician, there may be only the evidence of a meningeal localization. If the infection is a mild one it should respond readily to intraspinal therapy. All cases seen early, all with signs of an existing blood stream infection, and all severe cases should have the benefit of serum given intravenously.

SUMMARY

Thirty-one cases of meningococcus meningitis have been studied at Camp Lee during the past year.

Twenty-one, or 67.7 per cent., showed unmistakable evidence of a generalized infection before there was a localization in the meninges.

The mortality of the entire series was 22.6 per cent.

8. Dopter: Quoted J. A. M. A. **71**:35 (July 6) 1918.

During the period of intraspinous treatment alone and combined intraspinous and intrasubcutaneous treatment the mortality was 37.5 per cent.; during the period in which intraspinous and intravenous therapy was employed the mortality was 6.6 per cent.

CONCLUSIONS

Meningococcus meningitis, in probably every case, is primarily a generalized infection with subsequent meningeal localization.

The use of immune serum intravenously marks a great advance in the treatment of the disease.

Prolonged intraspinal treatment is very apt to result in permanent ill effects from the involvement of the cauda equina and nerve roots.

Intravenous treatment decreases the number of intraspinal treatments necessary, thus minimizing the harmful effects of local treatment.

One case is reported in which an active localized infection in the meninges recovered under intravenous therapy alone.

I am indebted to Major Tasker Howard, Chief of the Medical Service, for the opportunity of studying these cases and for his advice and criticism in the preparation of this report.

THE CHOLESTEROL CONTENT OF THE BLOOD IN VARIOUS HEPATIC CONDITIONS*

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In studying the hypercholesterinemia of cholelithiasis, a group of patients was encountered who had a continuous hypercholesterinemia.[1] Even after operation, at which all causes for an obstructive hypercholesterinemia were removed, these patients again became hypercholesterinemic with no discoverable basis for this condition.

In work previously published[2] we gave the evidence for believing that the liver is the regulator of the cholesterol metabolism of the body, the cholesterol being kept at a more or less constant level by excretion of cholesterol through the bile. It is of interest, therefore, to ascertain the cholesterol content of the blood of patients with various disorders of the liver usually associated with icterus.

In obstructive icterus due to cholelithiasis, we have almost invariably encountered a hypercholesterinemia of a rather severe grade. The amounts in the blood varied from 700 mg. to 250 mg. per 100 c.c. The degree of jaundice bore a definite relation to the amount of cholesterol in the blood, indicating that this cholesterinemia is due to the obstruction of the bile duct. However, we have encountered an occasional exception; a jaundiced patient with high temperature and infection will have a lower cholesterol content of the blood than a patient with the same degree of jaundice, but no active infection.

In other conditions associated with icterus, such as cirrhosis of the liver, acute yellow atrophy, pernicious vomiting of pregnancy, etc., the cholesterinemia bears no relation to the intensity of the icterus. The blood in fifteen cases of cirrhosis was examined and gave a maximum content of 0.24 per cent. and a minimum of 0.065 per cent. Only one patient of the fifteen showed a moderate hypercholesterinemia, the amount being 240 mg. per 100 c.c. The figures are as follows for each one of the fifteen patients:

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* From the Department of Physiological Chemistry, Pathological Laboratory, Mt. Sinai Hospital.

1. Rothschild, M. A., and Rosenthal, N.: The Dietetic Management of Hypercholesterinemia in Cases of Cholelithiasis, Am. J. M. Sc. **152**:394 (Sept.) 1916.

2. Rothschild, M. A.: The Relationship of the Liver to the Cholesterin Metabolism, Proc. New York Path. Soc., n. s. **14**:229 (Dec.) 1914.

Per cent.	Per cent.	Per cent.
0.24	0.15	0.125
0.185	0.147	0.105
0.182	0.137	0.1
0.162	0.134	0.075
0.15	0.129	0.065

All of these patients were jaundiced. The extent of jaundice in the cases showing only 0.105 per cent. was greater than in an obstructive cholelithiasis showing 0.64 per cent. The two cases showing the extremely low amounts, 0.075 and 0.065 per cent., were fatal cases, the patients dying three days after the blood examination.

TABLE 1.—Cholesterol Content of the Blood in Hepatic Disorders

Cirrhosis Per Cent.	Acute Atrophy Per Cent.	Pernicious Vomiting of Pregnancy Per Cent.	Carcinoma Per Cent.
0.24		0.177	0.4
0.185	0.116	0.164	0.36
0.182	0.1	0.127	0.25
0.162	0.087		0.185
0.15			0.166
0.15			0.162
0.147			0.146
0.137			0.142
0.134			0.125
0.129			0.124
0.125			0.094
0.105			0.09
0.1			
0.075			
0.065			

TABLE 2.—Cholesterol Content of the Blood in Other Icteric States

Banti's Disease Per Cent.	Splenomegaly with Icterus Per Cent.	Pernicious Anemia Per Cent.	Leukemia Per Cent.	Chlorosis Per Cent.
0.108	0.1	0.16	0.125	0.103
	0.095	0.155	0.112	
		0.155		
		0.152		
		0.145		
		0.136		
		0.125		
		0.125		
		0.1		
		0.075		

The explanation of these facts is extremely difficult. However, they suggest that in severe disturbances of hepatic function, there is a selective retention of bile pigments, while the cholesterol is not retained. In one case the bile was obtained at necropsy, and showed a rather high content of cholesterol, 0.12 per cent. against a normal content of 0.08 per cent.

In other conditions associated with icterus, such as primary or secondary carcinoma of the liver, or multiple abscesses, as seen in pylephlebitis, the cholesterol content of the blood is not proportionate

to the intensity of the jaundice. In carcinoma of the liver, we have encountered figures varying from 0.4 per cent., to 0.09 per cent.

We have examined the blood of three cases of acute yellow atrophy, and all showed a low blood cholesterin with extreme grades of icterus, the figures being 0.087, 0.1, and 0.116 per cent., respectively.

In three cases of pernicious vomiting of pregnancy with icterus, the figures were 0.177, 0.164 and 0.127 per cent., respectively. All of these cases gave evidence of hepatic disorder, as shown by urinary examination, and all three patients recovered. The blood was obtained toward the end of the disease. It is interesting that these cases showed no hypercholesterinemia, as one ordinarily finds in pregnancy. In the case showing 0.164 per cent. during the disease, a blood examination made two weeks after the patient was well, gave a figure of 0.248 per cent.

Other jaundiced conditions were investigated, those corresponding to the so-called hemolytic types, as seen in Banti's disease, pernicious anemia, chlorosis, leukemias and family splenomegaly with icterus. In all these conditions a normal or decreased content of the blood in cholesterol was noted. However, here we may be dealing with icterus of nonhepatic origin.

CONCLUSIONS

1. In obstructive icterus due to stones, etc., the cholesterol content of the blood is markedly elevated, and bears a definite relationship to the intensity of icterus.

2. In conditions associated with hepatic disorders, the cholesterol content of the blood is not increased, and is usually reduced. The cholesterinemia is not proportionate to the amount of bile pigments present in the blood.

3. In the so-called hemolytic icterus, there is no increase of blood cholesterol.

THREE CASES OF "RENAL GLYCOSURIA"*

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Of forty cases of supposed diabetes received at U. S. Army General Hospital No. 9, the following three proved to belong to the class of so-called "renal glycosuria." It was not possible under the circumstances to carry out a comprehensive research, and the observed facts are merely recorded as an addition to existing descriptions of the condition.

REPORT OF CASES

CASE 1.[1]—Private, infantry, American, 26 years of age, was admitted Nov. 1, 1918.

Family History.—The father died at the age of 78 from arteriosclerosis and apoplexy. The mother was drowned at the age of 65. Five brothers and one sister are alive and well. No inheritable disease is known to exist.

Personal History.—Patient had measles in childhood. He denies venereal or other diseases. Occasionally he drinks a glass of beer or wine; uses tobacco moderately. He has a normal figure. He has the average habits in diet. His occupation in civil life was shipping clerk. He enlisted May 8, 1917, and sailed for France August 7. He did full heavy duty without difficulty. He suffered somewhat from mustard gas in June, 1918, but did not report sick. In July he received a slight muscle wound in the left forearm from shrapnel and after a week in the hospital a small fragment was removed surgically. This shell exploded about thirty feet away and the patient received no special shock or fright. Glycosuria was discovered in the routine examination at this time. Symptoms of slight pruritus, polyuria, polyphagia, weakness and loss of weight were mentioned in the hospital, but no diet was prescribed and no such symptoms have been present before or since. October 16, he was sent back to America with a diagnosis of diabetes after complete surgical recovery.

Physical Examination.—The patient was a tall, well built, muscular young man, with the appearance and actions of perfect health. He was always cheerful and active; free from nervousness or peculiarities. A brown and tanned appearance of the skin over a large part of the trunk and arms was due to mustard gas. An irregular scar of healed shrapnel wound was evident on the left forearm. His teeth were in poor repair. The tonsils and throat were normal. Some palpable cervical lymph nodes were noted. The heart was normal in outline but irregular in rhythm. A diagnosis of incomplete heart block and auricular fibrillation was made by the cardiac service and was confirmed by electrocardiogram. The examination was otherwise negative.

Laboratory Examination.—The urine at admission was clear, amber in color, acid, specific gravity 1.036, containing sugar, but no acetone, albumin or casts, blood or other abnormalities. The Wassermann was negative. The blood

*From the diabetic service of U. S. Army General Hospital No. 9, Lakewood, N. J.

1. Lieut. L. G. Foster participated in the study of Case 1.

corpuscles numbered 4,700,000; the white blood corpuscles numbered 10,200; small mononuclears, 22 per cent.; large mononuclears, 10 per cent.; polymorphonuclear neutrophils, 63 per cent.; eosinophils, 5 per cent.

Treatment and Progress.—The observations made during most of the patient's stay in the hospital are contained in Tables 1, 2, 3 and 4.

1. INFLUENCE OF DIET

The patient was kept partly on weighed diets from the diabetic kitchen and was willing and faithful in all respects. During the periods indicated by "regular diet" he ate at the general hospital mess, and also patronized the canteen freely, like the other enlisted men. With the exception of December 9 and the tolerance tests, no special variations of the blood sugar on different diets were observed. The influence of the different components on glycosuria was observed as follows:

TABLE 1.—RESULTS OF URINE AND BLOOD EXAMINATIONS AFTER VARIOUS DIET MODIFICATIONS

Date	Diet			Urine			Plasma	Remarks
	Carbohydrate, Gm.	Protein, Gm.	Calories	Volume, C.c.	Glucose, Gm.	Nitroprussid Test	Sugar, per Cent.	
Nov. 2	125	125	1,100	960	Heavy	Negative	.....	Diet poor in fat
3	125	75	908	1,000	Heavy	Negative		
4	125	75	808	850	2.4	Negative		
5	125	75	808	1,380	6.76	Negative		
6	125	75	808	856	10.67	Negative		
7	Fast day			1,000	6.40	Negative		
8	Fast day			1,250	Negative	Negative	0.088	Blood taken 11 a.m. and 3 p.m.
9	Regular diet			1,100	13.00	Negative	0.100	Blood taken during digestion at 2:30 p.m.
10	Regular diet			1,080	Heavy	Negative		
11	Regular diet			975	Heavy	Negative		
12	0	150	801	1,350	Heavy	Faint		
13	0	150	801	1,250	4.63	Faint		
14	0	150	801	1,425	Heavy	Faint	0.098	Blood taken during digestion at 2:30 p.m.
15	0	150	801	1,400	Heavy	Faint		
16	0	150	801	650	1.50	Faint	0.080	Blood taken after breakfast; blood urea, 31.7 mg. per 100 c.c.
17	0	150	801	600	1.90	Faint		
18	0	150	801	400	3.00	Faint		
19	Regular diet			450	2.8	Faint	.....	Phenolsulphonephthalein test, 1st hour 35%; 2d hour 18%
20	Regular diet			1,350	23.70	Negative		
21	Regular diet			1,400	Heavy	Negative		
22	Regular diet			850	8.1	Negative		
23	Regular diet			625	6.4	Negative	0.080	Blood taken before breakfast
24	Regular diet			850	10.1	Negative		
25	Regular diet			700	9.3	Negative		
26	Regular diet			875	Heavy	Negative		
27	Regular diet			950	12.7	Negative		
28	Regular diet			675	10.5	Negative		
29	Regular diet			750	Heavy	Negative		
30	Regular diet			1,025	9.4	Negative		
Dec. 1	0	Unlimited		425	Heavy	Negative		
2	0	Unlimited		575	4.5	Negative		
3	0	Unlimited		650	4.92	Negative		
4	0	Unlimited		775	5.65	Negative		
5	0	Unlimited		275	1.90	Negative	.....	Urine partly lost
6	0	Unlimited		575	6.36	Negative		
7	0	Unlimited		675	8.47	Negative		
8	0	Unlimited		550	5.78	Negative		
9	0	Unlimited		500	3.70	Negative	0.136	Blood taken at 3 p.m.

TABLE 1.—Results of Urine and Blood Examinations after Various Diet Modifications—(*Continued*)

Date	Diet			Urine			Plasma	Remarks
	Carbohydrate, Gm.	Protein, Gm.	Calories	Volume, C.c.	Glucose, Gm.	Nitroprussid Test	Sugar, per Cent.	
Dec. 10	Fast day			800	3.05	Negative	0.096	Blood taken at 9 a.m.
11	Fast day			1,675	Negative	Negative		
12	0	Unlimited		3,535	16.46	Negative		
13	0	Unlimited		825	15.02	Faint		
14	Regular diet			850	25.08	Very faint		
15	Regular diet			975	14.93	Very faint		
16	Regular diet			1,425	Heavy	Very faint		
17	Regular diet			—	—	—		
18	Regular diet			550	8.75	Negative		
19	Regular diet			725	12.08	Negative		
20	Regular diet			700	5.00	Negative	.....	From December 21 to January 6 away on leave
Jan. 6	Regular diet			150	Heavy	Negative	.....	Urine partly lost
7	Regular diet			625	7.22	Negative		
8	Regular diet			1,200	16.41	Negative		
9	Regular diet			1,075	23.58	Negative		
10	Fasting after breakfast			645	7.31	Very faint		
11	Fast day			625	2.09	Very faint		
12	Fast day			1,325	2.12	Very faint		
13	Fast day			900	1.80	Moderate		
14	Fast day			825	1.65	Faint		
15	Fast day			1,255	Negative	Slight		
16	0	51.2	357	1,725	Moderate	Slight		
17	0	138.8	913	—	—	—	.....	Steak, 250 gm. diet for day
18	Regular diet after p.m.			750	8.41	Moderate	.....	Meat, 600 gm. diet for day, one meal
19	Regular diet			655	9.42	Negative		
20	Regular diet			800	15.71	Negative		
21	0	78.5	2,888	350	3.85	Negative	.....	Bacon, 100 gm., butter, 50 gm., egg yolk, 500 gm. in one meal (breakfast). Urine volume incomplete
22	Regular supper			475	11.30	Negative		

(*a*) *Influence of Carbohydrate.*—On low calory diets the glycosuria was apparently higher with carbohydrate included (Table 1, November 3, 4, 5 and 6) than with it excluded (Table 1, November 12 to November 18). With unlimited calories there was less glycosuria on carbohydrate free diet (Table 1, December 1 to December 9) than during the various periods of mixed diet. An exception is seen in the high excretion on carbohydrate free diet (Table 1, December 12 and 13) following fasting. The tolerance tests (Table 2) show the production or increase of glycosuria by glucose feeding.

(*b*) *Influence of Protein.*—Table 3 shows the production of glycosuria and on January 17 of hyperglycemia by eating beefsteak, but the effect is far less than that of preformed carbohydrate. The after-effect of different diets also seems significant. After a period of restriction to 125 gm. each of carbohydrate and protein, glycosuria ceased with two days of fasting (November 7 and 8). After a carbohydrate free period in which protein was eaten in large quantity, glycosuria also ceased with two fast days (December 10 and 11). After mixed diet with unlimited carbohydrate, five days of fasting was

TABLE 2.—Results of Glucose Tolerance Tests

Date	Time	Urine		Plasma Sugar, per Cent.	Remarks
		Volume, C.c.	Sugar, Gm.		
					Taken after fasting 2 days
Dec. 12	9:30 a.m.	500	Negative	0.09	Drank 200 c.c. water
	10:30 a.m.	205	Negative	.....	Drank 200 c.c. water
	11:30 a.m.	335	Negative	0.10	Drank 200 c.c. water
	12:30 p.m.	300	Negative	0.10	Given 100 gm. glucose in 200 c.c. water
	1:30 p.m.	160	0.88	0.214	Drank 200 c.c. water
	2:30 p.m.	370	6.66	0.320	Drank 200 c.c. water
	3:30 p.m.	535	4.82	0.200	Drank 200 c.c. water
	4:30 p.m.	260	2.34	0.170	Drank 200 c.c. water
	5:30 p.m.	125	0.66	.....	
	6:30 p.m.	170	Faint	0.130	Drank 200 c.c. water
	7:30 p.m.	40	Negative	—	Drank 200 c.c. water
	8:30 p.m.	90	Negative	0.090	
	9:00 p.m.	...	.....	.....	Ate all the bacon and eggs he could
	10 p.m. to 4 a.m.	400	1.04	.....	
					Taken after 3 days of regular diet
Dec. 17	9:30 a.m.	92	0.80	0.100	Given 100 gm. glucose in 200 c.c. water
	10:30 a.m.	74	2.36	0.106	Drank 200 c.c. water
	11:30 a.m.	65	1.76	0.080	Drank 200 c.c. water
	12:30 p.m.	65	0.27	0.070	Drank 200 c.c. water
	2:30 p.m.	150	0	0.079	Drank 200 c.c. water
	5:30 p.m.	...	....	0.090	
					Taken 5 days after fasting and 2 days on carbohydrate-free diet
Jan. 18	9:30 a.m.	200	0.90	0.088	Given 100 gm. glucose in 200 c.c. water
	10:00 a.m.	—	—	0.167	Drank 200 c.c. water
	10:30 a.m.	300	3.00	0.214	Drank 200 c.c. water
	11:30 a.m.	200	9.00	0.185	Drank 200 c.c. water
	12:30 p.m.	300	4.29	0.136	Drank 200 c.c. water
	1:30 p.m.	255	1.15	0.116	Drank 200 c.c. water
	2:30 p.m.	150	0.44	0.088	
					Taken after 2 weeks of regular diet
Feb. 3	9:30 a.m.	105	Moderate	0.107	Given 100 gm. glucose in 200 c.c. water
	10:00 a.m.	150	Moderate	0.133	
	10:30 a.m.	25	Heavy	0.142	
	11:30 a.m.	None	—	0.158	
	12:30 p.m.	50	Heavy	0.101	
	1:30 p.m.	35	Heavy	0.086	
	5:00 p.m.	80	Moderate	0.115	

TABLE 3.—Results of Protein Tests

Date	Time	Urine		Plasma Sugar, per Cent.	Remarks
		Volume, C.c.	Sugar, Qualitative Test		
Jan. 16	9:35 a.m.	200	Faint	0.100	Two bloods fasting and urines for the period. At 12 noon fed protein meal, 250 gm. steak
	10:45 a.m.	106	Negative	0.102	
	12:00 noon	32	Negative	—	
	12:55 p.m.	88	Slight	0.097	
	1:35 p.m.	325	Slight	0.115	
	2:35 p.m.	175	Slight	0.107	
	3:35 p.m.	250	Negative	0.122	
	5:00 p.m.	150	Negative	0.075	
Jan. 17	8:30 a.m.	90	Faint	0.094	Two bloods fasting and urines for the period. At 10:20 a.m. fed protein meal, 600 gm. steak
	9:30 a.m.	40	Faint	0.113	
	10:20 a.m.	40	Faint	0.106	
	11:20 a.m.	40	Faint	0.114	
	12:30 p.m.	90	Slight	—	
	1:30 p.m.	98	Slight	0.140	
	2:30 p.m.	135	Slight	—	
	3:30 p.m.	85	Slight	0.129	
	4:30 p.m.	90	Slight	—	
	5:30 p.m.	100	Slight	0.124	
	7:30 p.m.	95	Slight	—	
	8:30 p.m.	—	—	0.109	

necessary before sugar freedom was attained January 15. Hypothetically, the smaller immediate effect of protein is explainable on the assumption that not all the carbohydrate theoretically derivable from it is necessarily formed from it in metabolism, and the smaller after effect by the well-known fact of the smaller glycogen storage from protein as compared with carbohydrate. The observation is interesting as indicating that stored material affects the glycosuria.

TABLE 4.—RESULTS OF FAT FEEDING EXPERIMENT*

	January 21			Remarks
	8:45 a.m.	12:30 p.m.	3:30 p.m.	
Plasma sugar, per cent.	0.105	0.100	0.100	9 p.m. finished large fat meal consisting of bacon, 100 gm.; butter, 50 gm.; egg yolks, 500 gm. Urine up to 10 p.m.: volume, 350 c.c.; sugar, 3.85 gm.
Corpuscle sugar, per cent.	57.8	48.5	46.0	
Qualitative lipemia	Negative	Faint	Slight+	
Total fat:				
Whole blood, per cent.	0.62	0.78	0.79	
Plasma, per cent.	0.84	0.90	0.84	
Corpuscles, per cent.	0.68	0.67	0.74	
Total fatty acid:				
Whole blood, per cent.	0.51	0.54	0.52	
Plasma, per cent.	0.59	0.64	0.60	
Corpuscles, per cent.	0.46	0.43	0.44	
Cholesterol:				
Whole blood, per cent.	0.24	0.25	0.25	
Plasma, per cent.	0.25	0.26	0.24	
Corpuscles, per cent.	0.22	0.24	0.26	
Lecithin:				
Whole blood, per cent.	0.48	0.45	0.45	
Plasma, per cent.	0.45	0.45	0.43	
Corpuscles, per cent.	0.50	0.45	0.48	

* Total fat, cholesterol and lecithin are determined directly. Total fatty acid = fat — cholesterol (Bloor).

(*c*) *Influence of Fat and Total Calories.*—No experiments with pure fat or alcohol ingestion were performed. The disappearance of glycosuria on fasting is more probably explained by the simple withdrawal of carbohydrate than by a fall in total metabolism. In comparing differing diets it is seen that the glycosuria in the low calory period (Table 1, November 3, 4, 5 and 6) is fully as high as could be expected in comparison with the periods of unrestricted diet, considering the much larger carbohydrate intake in the latter; and on carbohydrate free diets the glycosuria in the low calory period (Table 1, November 12 to November 18) compares well with that in the high calory period (Table 1, December 1 to December 9), considering the larger quantities of protein eaten in the latter. Therefore, as far as the observations permit judgment, there is no indication of an influence of the total caloric ration, aside from the portion represented by the direct carbohydrate forming foods.

2. PLASMA SUGAR

This was determined by the Benedict method, and was regularly below or near 0.1 per cent. Fractional urine specimens were taken so often as to leave no doubt that glycosuria actually occurred at this

level. Protein ingestion or carbohydrate free diet seemed to create a tendency to hyperglycemia. The single high blood sugar of Table 1, December 9, occurred on carbohydrate free diet. Other observations are mentioned in the two following paragraphs.

3. GLUCOSE TOLERANCE (TABLE 2)

The patient took 100 gm. glucose on an empty stomach on occasions when the diets of the preceding days had been different. December 17, after three days of ordinary mixed diet, there was no rise, but instead a slight fall in the plasma sugar. February 3, after two weeks of mixed diet, the curve rose to about a normal height, but was atypical in that the peak came at the end of two hours. December 12, after fasting, the behavior was radically different and the hyperglycemia reached 0.320 per cent. January 18, after carbohydrate free diet, there was again hyperglycemia, but to a less marked degree. The two curves first mentioned are uncommon, but not peculiar to this condition. They represent some abnormality in the patients who show them, but whether this pertains to absorption or metabolism is not always clear. The hyperglycemia in the two curves last mentioned is nothing extraordinary. The increased tendency to hyperglycemia and glycosuria resulting from fasting is a long familiar fact, and there are a few observations of a similar effect of carbohydrate free diet. No confusion should exist between this and the other fact that fasting and carbohydrate free diet are used to increase the carbohydrate tolerance in diabetes. The carbohydrate sensitiveness of the normal fasting organism is a trivial phenomenon, evidently expressing nothing more than some state of temporary unpreparedness for the carbohydrate flood. The actual assimilation of carbohydrate is limited only by the dose. In diabetes carbohydrate metabolism is fundamentally impaired, and is strengthened through the rest afforded by carbohydrate free diet and still more by fasting.

4. PROTEIN INGESTION

On January 16 (Table 3) 250 gm. beefsteak gave rise to slight glycosuria without hyperglycemia. January 17, 600 gm. steak caused a more distinct rise of blood sugar, but the glycosuria was still too slight to warrant titration by ordinary methods. December 12 and 13 (Table 1) there was exceptionally high glycosuria with carbohydrate free diet, presumably because the patient either ate more protein or was sensitized to it by the preceding fast.

5. RENAL THRESHOLD

It would have been desirable to make a more detailed study of this point, but the existing observations are opposed to the idea that the blood sugar level was the sole factor determining either the occurrence or the quantity of sugar excretion. In the tolerance tests this was evidently greatest when the blood sugar was high (Table 2), but was higher January 18 than December 12, though the hyperglycemia was higher December 12. In Table 3, it is evident that the qualitative urinary reactions do not correspond accurately to the levels of blood sugar; also the excretion was trivial throughout, though the blood sugars after these protein meals were often higher, notably January 17, than during the marked glycosuria of the glucose tests, especially December 17.

6. URINE VOLUME

On the whole, there was oliguria, sometimes so marked that the patient was led to inquire about it himself. No indication was found of any cause other than a failure to drink. Whenever more fluid was taken on instructions or accidentally, the twenty-four hour urine increased in proportion, and the body weight never indicated fluid retention.

7. GLUCOSE AND WATER DIURESIS

In Table 1 no relation is perceptible between the volume and sugar content of the urine, in the sense either of polyuria or oliguria caused by sugar, or a flushing out of more sugar by increased urinary volume. In the glucose tests (Table 2) the water intake was regulated except February 3. The two tests with hyperglycemia showed the following: December 12 a fall in urine volume accompanying the hyperglycemia and slight glycosuria of the first hour after the glucose dose; in the ensuing hours polyuria, roughly parallel to the hyperglycemia, but not to the urinary sugar; then marked oliguria after hyperglycemia and glycosuria had subsided. January 18, less hyperglycemia and less polyuria, though the urinary sugar was greater than December 12, and a less marked diminution of urine after the blood sugar had fallen. December 17, with no hyperglycemia, but moderate glycosuria (the percentages of urine sugar running higher than December 12) there was striking oliguria, with a moderate increase in volume in the 2:30 p. m. specimen when glycosuria had ceased, the whole experiment being characterized by water retention even exceeding that of normal persons. In general, therefore, the urine volume seemed to be influenced by the blood sugar but to be independent of the urinary sugar.

8. RENAL FUNCTION (TABLE 1)

The blood urea of 31.7 mg. per 100 c.c. November 16 is a noticeably high figure, though probably affected somewhat by the carbohydrate free diet. November 19 the phenolsulphonephthalein elimination was 35 per cent. in the first hour and 18 per cent. in the second hour.

9. CHARACTER OF SUGAR EXCRETED

Fresh urine samples were taken, along with those from patient No. 2, to Dr. P. A. Levene, who prepared and identified glucosazone, and excluded the presence of disaccharids, levulose, pentoses and glycuronic acid. In this hospital, the routine reduction tests with Benedict's solution were sometimes fairly normal in appearance, sometimes slow and atypical. In titration with Benedict's quantitative reagent the end points were satisfactory. Fermentation with Fleischmann's yeast was prompt and complete in tests made at intervals throughout the stay in hospital, except for one short period when a few negative or incomplete fermentations were obtained. These were not thoroughly controlled, and may therefore represent mistakes of some kind.

10. BLOOD LIPOIDS

According to Bloor, normal fasting blood contains, in whole blood, plasma and corpuscles, respectively, as a maximum 0.41, 0.43, 0.45 per cent. fatty acids; 0.25, 0.31, 0.23 per cent. cholesterol, and 0.33, 0.26, 0.44 per cent. lecithin.

Table 4 shows that the cholesterol was normal in this patient, not elevated as in the more severe grades of true diabetes. It did not increase during digestion of a meal rich in cholesterol. The lecithin was elevated to a degree comparable with many diabetic cases, but failed to rise during digestion. The fasting values for total fat and fatty acids are normal, but the absence of a digestive increase is remarkable. A slight turbidity of the plasma developed during digestion, but Bloor and Gray have shown that this is not a reliable index of chemical lipemia.

CASE 2.—Lieutenant, ammunition transport service, American, married, aged 42, was admitted Nov. 1, 1918.

Family History.—Father, mother and one brother are well. There was no history of inheritable disease in family.

Personal History.—Patient had measles, mumps, chickenpox, scarlet fever and whooping cough in childhood; diphtheria in 1892; no other infections. He had no venereal diseases. He used no alcohol, and tobacco only in moderation. He subsisted on an ordinary diet. He had been an investment banker in civil life and lived under the best hygienic conditions. He had a nervous temperament, but never manifested it to a marked degree. He was a member of the National Guard, and served three years in the Philippines, where

he sustained a Mauser bullet wound of the right leg in 1900. This healed uneventfully. He resumed civil occupation until commissioned a first lieutenant, May 10, 1917, and after doing full duty in this country for a year went overseas in May, 1918.

Present Ailment.—July 27, 1918, the patient was bringing up several truck loads of small arms ammunition to the battle line at Chateau Thierry, he himself sitting beside the driver on one of the trucks. They were located by a German aeroplane and the entire convoy was destroyed by a heavy concentration of artillery fire, the patient and two other badly wounded men being the only ones to escape alive. The high explosive shell which wrecked his truck killed the driver and hurled the patient to a considerable distance. While being carried to a French evacuation hospital he was wounded with shrapnel and gassed with phosgene. His surgical injuries included superficial wounds and abrasions of feet, hands and back, and severe concussion, especially of the base of the spine, on which he apparently had landed when blown from the truck. He was unconscious for three days. Thereafter his mind was clear, with no hallucinations or loss of memory, but he was weak, and suffered much pain, especially on attempted movements. He was extremely nervous and apprehensive, and had extreme tremor and incoordination, especially when nervous, the muscles of speech being involved like those of the extremities. This condition continued with little improvement, while the patient was moved from one hospital to another. Finally, he was given careful examination at a base hospital, where glycosuria was found and the diagnosis of traumatic diabetes was made, which was assumed as a factor in his unfavorable progress. After confirmation of the diagnosis by higher staff officers in another hospital, the patient was sent to America, Oct. 9, 1918. Important in connection with the glycosuria is the fact that the urine was found free from sugar when the patient received his commission and again when he was examined for overseas duty. Also, in civil life he had been intimate with a young physician, who for incidental reasons had repeatedly tested the urine and found no sugar or other abnormalities. Also after the injury glycosuria is said to have been absent sometimes, generally slight, and heavy especially when there was nervousness.

Physical Examination.—The patient is rather short and stout, 5 feet 6 inches in height, weighing ordinarily 160 pounds (now the same). He has an excellent color and a generally healthy appearance, except for nervous manifestations. The general examination is negative. The pupils are equal and react normally to light and distance. The knee and other reflexes are exaggerated, the response sometimes being in the form of clonus. The patient can barely stand and walk with the aid of an attendant and a cane. The stooped posture, gross tremor of the limbs, and shuffling unsteady gait are much like paralysis agitans. He is emotional and excitable ordinarily, and hesitates somewhat in speech because of difficulty both in finding and in forming words. Any sudden noise, such as a fire gong, an automobile horn, or even the slamming of a door, throws him into a panic of helplessness and tremor, in which he is powerless to control his muscles or utter an intelligible word. Even more than of the incoordination and nervousness, he complains of pain in different parts of the body, particularly along the spine, also of headache and insomnia. Orthopedic examination showed tenderness of both muscles and bones in the affected regions, but no displacements, atrophies or other definite abnormalities.

Laboratory Examination.—The urine at admission was of a clear amber color, acid, specific gravity, 1.025; containing a copper reducing substance, but negative for albumin, acetone and indican. The sediment showed microscopically a little epithelium and amorphous material, no casts. Later urine specimens were tested repeatedly in the hospital and were the same in general character. The blood Wassermaan was negative.

Treatment and Progress.—The patient was admitted late in the afternoon of October 25, after having taken a full mixed diet up to that time. He received only soup, coffee and two bran-agar muffins for supper, and the same for breakfast the next morning. The moderate sugar reaction present at admission diminished to a trace, but the copper reduction was slow and atypical. It being suspected that the case was not a true diabetes, the fasting program was broken off by a test meal at noon, high in carbohydrate (cereal, milk, sugar, egg, potatoes, bread, butter, jam). The quantities were not measured, but the patient, being hungry, ate heartily. The analyses disclosed the following findings:

TABLE 5.—Plasma and Urine Sugar in Relation to Eating

Time	Plasma Sugar, per Cent.	Urine Sugar
Before eating	0.125	Trace
One hour after eating	0.145	Faint
Three hours after eating	0.144	Slight
Five hours after eating	0.114	Faint

One probable cause for the hyperglycemia was a fire drill in the forenoon, the acute panic and helplessness aroused by the gong being followed by great nervousness during most of the day. Possibly also the preceding fast tended to increase the hyperglycemia following carbohydrate ingestion. The patient was extremely desirous of visiting friends in New York, and as the indications were against diabetes, he was allowed to go on a short leave, in the hope that his nervous condition might be improved.

He returned November 1 much worse in his nervous condition from the excitement of the city. On a full mixed diet, moderate to heavy copper reduction tests were present in every urine voiding of every day. No blood samples were taken till the nervousness had abated somewhat. Then, November 5, the plasma sugar was 0.111 per cent. before breakfast, and November 8 it was 0.100 per cent. two hours after a carbohydrate rich breakfast. Also, November 5 a test was made with 25 gm. glucose in 150 c.c. solution, taken on an empty stomach in the morning.

TABLE 6.—Plasma and Urine Sugar as Influenced by Glucose Ingestion

Time	Plasma Sugar, per Cent.	Urine	
		Volume, C.c.	Sugar
Before glucose	0.111	140	Slight
One hour after glucose	0.111	32	0.26 per cent.
Two hours after glucose	0.135	57	Moderate
Three hours after glucose	0.084	22	Faint

Beginning November 12, a trial was made of a low calory, carbohydrate-free diet as follows:

TABLE 7.—URINARY FINDINGS AFTER LOW CALORY CARBOHYDRATE FREE DIET

Date	Diet			Urine		
	Carbohydrate	Protein	Calories	Volume, C.c.	Sugar, Gm.	Nitroprussid Test
Nov. 12	0	80	589	1,000	Moderate	Faint
13	0	150	803	1,200	Slight	Faint
14	0	150	803	2,250	Faint	Faint
15	0	150	803	1,200	2.4	Faint
16	0	150	803	640	Heavy	Slight
17	0	150	803	650	1.14	Faint
18	0	150	803	610	0.34	Slight
19	0	150	803	400	0	Moderate
20	Full mixed diet, unweighed			925	13.32	Faint
21	Full mixed diet, unweighed			500	5.65	Negative
22	Full mixed diet, unweighed			1,150	8.1	Negative
23	Full mixed diet, unweighed			1,225	6.37	Negative
24	Full mixed diet, unweighed			1,150	8.81	Negative
25	Full mixed diet, unweighed			1,000	5.17	Negative
26	Full mixed diet, unweighed			750	4.1	Negative
27	Full mixed diet, unweighed			1,300	3.6	Negative
28	Full mixed diet, unweighed			975	4.23	Negative
29	Full mixed diet, unweighed			1,475	3.00	Negative
30	Full mixed diet, unweighed			Incomplete	0	Negative
Dec. 1	Full mixed diet, unweighed			1,450	Heavy	Negative
2	Full mixed diet, unweighed			Incomplete	Heavy	Negative
3	Full mixed diet, unweighed			600	Heavy	Negative

Two plasma sugar tests were taken during the period of carbohydrate free diet, between 9 and 10 a. m. in each instance (during digestion of breakfast). The result was 0.078 per cent. November 14, and 0.094 per cent. November 16. Sugar reactions were present in the urine for the periods represented by the blood samples—faint November 14, moderate to heavy November 16. There is thus some indication of a renal threshold. Throughout the period of observation, the urine was examined in at least four divisions in every twenty-four hours (according to the routine of the diabetic service). Sugar was constantly present, except on three occasions. One of these was the full day November 19, after a week of low calory carbohydrate free diet; another was November 30 on full mixed diet, the test covering not quite the entire day, one period being lost. The third time sugar was absent was a single specimen on another date, on which other specimens contained considerable sugar. On a mixed diet shortly before leaving the hospital, the plasma sugar was 0.096 per cent. January 8, and 0.080 per cent. January 11.

The urinary sugar regularly showed certain peculiarities. In the qualitative test with Benedict's copper reagent, the reduction was unusually slow in coming, and then often appeared much heavier than usual with slow tests. The character of the reduction was atypical, with a strong tendency to formation of the red or black oxids, so that this patient's test could generally be picked out at a glance from among the tubes of diabetic tests in the same rack. Titration with Benedict's

quantitative reagent indicated lower percentages than would have been expected from the final appearance of the qualitative tests, and the end point was always indistinct and sometimes impossible to find. On account of this difficulty, and the doubtful nature of the sugar, attempts at quantitative estimation were frequently omitted. Many fermentation tests were carried out with Fleischmann's yeast, with the invariable result of no gas formation, or only traces, and little or no change in the reducing properties, whereas glucose added to the same urine fermented promptly and apparently completely. As far as could be observed, these peculiarities remained the same on either a mixed or carbohydrate free diet.

Urine samples preserved with toluene, less than twenty-four hours old, were taken to Dr. P. A. Levene, being out of the ice-box only for about three hours on the trip from Lakewood to New York. He immediately observed the slow atypical reduction with Fehling's solution, and also performed tests which excluded the presence of pentoses, disaccharids, levulose and glycuronic acid. Circumstances then brought it about that the urine remained several weeks in the ice-box before further testing. Dr. Levene then performed osazone tests, and identified glucosazone by its crystals and melting point.

Other urine samples were similarly taken to Dr. Stanley R. Benedict, who found the sugar fermentable with yeast, and obtained a comparison of titration and polarimetric readings approximating the theoretical for glucose. He also prepared and identified glucosazone. (For other findings, see below.)

The patient's urine record in France was never obtained, but he stated that the reduction tests had frequently been negative there, and appeared or increased markedly with nervous attacks. His nervous and general condition rapidly improved in Lakewood with the aid of rest and physicotherapy, but the reducing properties of the urine persisted unchanged. When his recovery was almost complete, he was granted a thirty days' leave, which he spent at rest and quiet recreation in the country. He returned to the hospital free from all symptoms, except a slight nervousness of manner, and on his request he was discharged Jan. 22, 1919, to undertake quartermaster duty in New York. Notwithstanding the other improvement, the reduction test was positive in every specimen of urine the same as before.

Under the strain of work and excitement the patient broke down nervously, and was admitted to another military hospital. He improved more rapidly than before, was discharged from the army with no compensation for disability, and is now in civilian employment in New York. On advice, he reported several times to the laboratory of Dr. Benedict, who, with the fresh urine, found fermentation tests negative

or very incomplete, and other tests indicating a substance other than glucose. The problem of identification may be pursued further by Dr. Benedict, if circumstances permit.

CASE 3.—The wife of an army officer, American, aged 43 years, was admitted March 12, 1919.

Family History.—Her father died at 63 years of age from perforated gastric ulcer. Her mother is alive, but an invalid with rheumatism. One sister died when 18 months of age of unknown cause. One brother and three sisters are alive and well, though one of the sisters is obese. No inheritable disease is known in the family.

Personal History.—The patient had whooping cough, measles and chicken-pox in childhood, no other illness. She had two pregnancies, the first a premature birth with face presentation. There were no postpartum disturbances. She uses neither alcohol nor tobacco; has no excesses in food or sweets, but admits a tendency to become obese recently, so that she would like to reduce for the sake of both looks and comfort. She is not constipated. She spent two years in the Philippines when her husband was in campaign there; otherwise she has lived the usual army life in this country under good hygienic conditions. Her husband has been in France for the present war, and she has tried to be of service and also suppress worry by prolonged heavy work in relief organizations.

Present Ailment.—After the signing of the armistice, she experienced marked continuous lassitude, also slight pruritus and loss of weight. This led to a medical examination, which revealed glycosuria, and she came for treatment because of the diagnosis of diabetes rather than on account of any distressing symptoms.

Physical Examination.—She is 5 feet 9 inches tall and weighs 175 pounds. She has the appearance of perfect health and slight overweight. Her blood pressure is 125 systolic, and 75 diastolic. The examination was entirely negative, except for her heart. The heart was normal in size to physical and fluoroscopic examination, and its function was apparently normal, but there was a short systolic murmur in the aortic area, and electrocardiograms were interpreted to indicate a rotation of the organ to the right. Roentgenograms did not reveal any rotation.

Laboratory Examination.—The Wassermann was negative. A blood count was not made. The urine was normal to routine tests, except for sugar.

Treatment and Progress.—The patient was admitted on the afternoon of March 12, and was immediately started on the usual diabetic fasting program of soup, coffee and bran biscuits. Sugar freedom was attained March 13, the charted excretion of 0.83 gm. being only for the fore part of that day. When a carbohydrate tolerance test was attempted with green vegetables, a faint reducing reaction promptly returned and increased as the carbohydrate was increased. Table 9 gives the general record.

TABLE 8.—RENAL FUNCTION TESTS

	Blood Urea, Mg. per 100 C.c.	Phthalein Test	
		First Hour, per Cent.	Second Hour, per Cent.
Nov. 16	22.2		
Nov. 19	—	35	19

TABLE 9.—The Urine and Blood Findings with Various Diets in Case 3

Date 1919	Diet: Carbohydrate, Gm.	Diet: Protein, Gm.	Diet: Calories	Urine: Volume, C.c.	Urine: Glucose, Gm.	Urine: Nitroprussid Test	Plasma Sugar, per Cent.	Remarks
Mar. 12	Admission			175	Heavy	Moderate		
13	Broth, bran, coffee			500	0.83	Heavy	0.100	Fasting blood sugar
14	25	8.6	154	775	Faint	Heavy	0.100	Fasting blood sugar
15	50	12.3	269	700	Slight	Heavy		
16	75	15.2	387	355	1.39	Heavy		
17	100	16.9	510	445	Moderate	Moderate	0.122	Blood 2 hours after noon meal
18	7.5	0	30	450	Very faint	Moderate		
19	General hospital diet from now on			875	7.00	Heavy		
20				800	11.58	Slight		
21				1,000	9.20	Negative		
22				825	Heavy	Negative		
23				800	Heavy	Negative		
24				1,025	Heavy	Negative	0.107	Blood 2 hours after breakfast
25				1,150	Heavy	Negative		
26				825	Heavy	Negative	0.117	Blood 2 hours after noon meal
27				1,250	Heavy	Negative		
28				375	Heavy	Negative	.....	Urine for only one period
29				975	Heavy	Negative		
30				.....	.....	.....	0.113	Blood 1½ hours after breakfast

TABLE 10.—Results of Glucose Tolerance, Phenolsulphonephthalein and Mosenthal Fixation Tests in Case 3

Date	Time	Urine: Volume, C.c.	Urine: Sugar, Gm.	Urine: Nitroprussid Test	Plasma Sugar, per Cent.	Remarks
Mar. 19	9:30 a.m.	125	Negative	Moderate	0.113	Fasting blood sugar. Given 100 gm. glucose in 200 c.c. of water
	10:30 a.m.	77	2.4	Faint	0.139	Drank 200 c.c. of water
	11:30 a.m.	143	3.6	Negative	0.125	Drank 200 c.c. of water
	12:30 p.m.	675	2.1	Negative	0.115	

	Phenolsulphonephthalein Test	Date	Blood Urea, Mg. per 100 C.c.	Urea Index
Mar. 24	First hour.....35.6 per cent. Second hour.....28.2 per cent.			
	Total.....63.8 per cent.	Mar. 17 Mar. 30	18.62 15.77	188

Mosenthal Fixation Test

Time	Urine: Volume, C.c.	Urine: Sp. Gr.	Urine: NaCl, Gm.	NaCl, per Cent.	Remarks
Mar. 31 10 a.m.	190	1.028	2.21	1.16	Breakfast, 8 a.m.; dinner, 12 noon; supper, 5:30 p.m.
12 noon	100	1.030	1.56	1.56	
2 p.m.	102	1.035	1.39	1.36	
4 p.m.	200	1.030	2.88	1.44	
6 p.m.	88	1.035	1.35	1.54	
8 p.m.	112	1.034	1.50	1.34	
Night	380	1.024	4.10	1.08	
	1,172		14.99		

GENERAL DISCUSSION

A review of the literature is omitted, because it has been covered by several recent authors, and also because the facts do not yet afford a simple or harmonious conception of the condition. Certain deductions in connection with the present group of three cases suggest themselves as follows.

1. INCIDENCE

As the most important characteristic of this anomaly is the excretion of glucose or a glucoselike substance with a normal or low level of blood sugar, the introduction of simple methods of blood sugar analysis within the past few years has permitted a more extensive and accurate investigation than was possible before. The considerable number of wholly or partially demonstrated cases reported in this time has established firmly the existence of such a condition, and has also indicated that it is not actually a rarity. The proportion of three "renal" cases to thirty-seven of true diabetes in this hospital is surprisingly and perhaps exceptionally high, but interesting in view of the random selection of patients, who were simply those soldiers in whom some military officer happened to diagnose glycosuria. The odds were thus strongly in favor of true diabetes, because young diabetics ordinarily show symptoms leading sooner or later to the diagnosis, while the vast majority of enlisted men never had a urine examination at any time, and because of the absence of symptoms the "renal" cases could be discovered only in that small minority who were subjected to urinalysis for some other cause. Doubtless some of the examples of atypical or "harmless" diabetes which formerly puzzled clinicians were actually "renal" in character, and the recognition of this group will reduce the number of diabetic cases in which it is imagined that diet may be neglected with impunity. Life insurance statistics furnish the best evidence against the existence of abnormal glycuresis in any high percentage of the population, but they are imperfect because of the usual lack of blood analyses; the latter may sometimes be necessary for this purpose in the future. It is of some interest for comparison that no cases of levulose, pentose or glycuronic acid excretion were found in this service.

2. ETIOLOGY

A. General Physical Condition.—No constant relation was discoverable between the urinary anomaly and anything in the physical examination of the patients. Patient No. 1 had a remarkable cardiac disturbance, which appeared serious in examination, but had never caused subjective symptoms. Patient No. 3 had the suggestion of a slight cardiac rotation, according to electrocardiographic examination.

But the heart and circulation of patient No. 2 were normal, unless the nervous shock was responsible for some functional change not revealed by examination. Otherwise all three patients appeared to be in very good physical condition. Patient No. 1 had been slightly, and patient No. 2 more seriously exposed to mustard gas, but the woman, patient No. 3, had remained safe in this country.

B. Nervous System.—Patient No. 2, when first admitted, seemed to furnish something which had been awaited with curiosity throughout the whole duration of the diabetic service, namely, a case of diabetes due to war injury. There was a history of repeated urine examinations showing absence of glycosuria up to induction into service, then a tremendous shock and trauma, followed by persistent sugar excretion. But this, the only traumatic case seen, turned out to be of the "renal" type, and it thus appears as though this condition here had been caused by traumatism and nervous shock. Such an occurrence, if positive, is important as the only known example of definite causation of this anomaly by this or any other means, for certain cases in the literature seem to have been congenital, but in the great majority the time and mode of origin have been entirely unknown. Patient No. 3 in the present series had had some worry and strain, but patient No. 1 was a happy-go-lucky individual, who had suffered no shock or important injury, and was the reverse of neurotic in nature. There is no information whether the urinary condition in these two patients was congenital, or as to the time or cause if it was acquired.

C. Kidneys.—The first writers on this condition regarded it as associated with nephritis, and thus seemingly on a par with the occasional glycosuria in animals poisoned with uranium, chromium, etc. The more recently reported cases, including the great majority and the ones most thoroughly studied, have been independent of albuminuria or known renal lesions, past or present. But the name "renal glycosuria" still carries with it the assumption that the seat of the anomaly is in the kidney. None of the three patients in this series had albumin, casts or blood in the urine, or gave any history of nephritis, unless the kidneys of two of them might have been irritated by mustard gas. The blood urea was slightly elevated in patient No. 1, normal in the other two. The index of urea excretion was normal in all three, and the Mosenthal fixation test was normal in the only one (No. 3) in whom this test was made. On the other hand, the phenolsulphonephthalein elimination of all three of these patients was slightly low. The phenolsulphonephthalein tests were carried out in the general laboratory of the hospital, by the same workers and with the same technic as all the tests of this sort in the hospital. The poor phenolsulphonephthalein function of these three patients may, perhaps, be only

a peculiar coincidence, but suggests the desirability of similar tests in other cases of this kind. It may be worth while also to call attention to the entire lack of necropsies in such cases, and the interest attaching to any that may be obtainable, for questions not only of ordinary renal pathology, but also (if the glycosuria continues to death) of the Armanni or Ehrlich vacuolation and glycogenic infiltration which is a regular feature of severe diabetes and phloridzin glycosuria.

3. PROGNOSIS

In certain instances in the literature the continuance of "renal glycosuria" for many years has been proved, and apparently no case has ever been described in which it is known to have ceased. On the other hand, it is reckoned as harmless, and no known injury has resulted from it in any reported case. Even in the few cases of greatest severity in the literature, in which the sugar excretion has been so great as to be comparable to true diabetes and to cause danger of acidosis when carbohydrate was restricted, it was only necessary for the patient to take a sufficiently liberal carbohydrate diet to be free from all disagreeable symptoms, except sometimes polyuria. This condition thus furnishes interesting evidence that the weakness and other disturbances of health in true diabetes are not due solely to the loss of sugar from the body. The importance of a clear distinction in definition between diabetes and glycosuria (or glycuresis—Benedict) is also thus emphasized. The observations in the present three cases conform to the foregoing statements concerning the prognosis.

4. URINE VOLUME

As mentioned, polyuria has characterized some cases in the literature, particularly when the sugar output was large. Inspection of the tables for these three patients shows that there was never an excessive urinary volume, but sometimes, on the contrary, a marked oliguria. There was never any appreciable fluid retention, and the elimination was proportionate to the intake, the patients merely saying that they had no desire to drink. This behavior is not altogether exceptional, as the sugar excretion, on the whole, was rather low, and it is well known that in certain cases of true diabetes the urine volume for some reason fails to show the usual increase. In a few glucose tolerance tests, however, the fluid relations observed were of some interest. Patient No. 3, for example, receiving 100 gm. glucose March 19, had considerable sugar percentages in the urine, but the urine volume was in inverse relation, the marked polyuria of 675 c.c. in the third hour coinciding with the lowest percentage of reducing substance. The peculiarities of diuresis in the tolerance tests of patient

No. 1 were mentioned in the description of that case. The influence of hyperglycemia seemed to be opposite in the two cases. There might be a chance of instructive comparisons of the urine volume in true diabetes with hyperglycemia, and that in "renal" cases with, perhaps, equal glycuresis and either elevated or normal blood sugar, except for our ignorance of the mechanism and even of the exact nature of the reducing substance in the latter cases. The one general conclusion which can be drawn from all three of the present cases is that the sugar excretion and the water excretion, on the whole, behave as separate functions. Increase of sugar does not necessarily increase the urine volume, and increased water elimination has no appreciable influence in sweeping out an additional quantity of sugar.

5. METABOLISM

A. Fat Metabolism.—On the whole, especially in Patients No. 1 and 2, acetonuria was conspicuous by its absence. It was present sometimes with fasting or restricted diet, but only to the extent of slight or moderate urinary reactions; a positive nitroprusside test in the blood plasma or lowering of the CO_2 capacity was never observed, and also no subjective symptoms. Acetonuria was distinctly more prompt and marked in Patient No. 3, but the difference is readily explainable by her slight obesity. Differences of this order are the familiar experience with both normal persons and patients with true diabetes. In none of the three cases of this series was there any sign of unusual tendency to acidosis, either as a specific phenomenon or in consequence of the loss of sugar.

A few estimations of blood lipoids were performed in Case 1 on the chance of detecting any abnormalities; but though the lecithin values were high, and the absence of digestive hyperlipemia seemed comparable with the absence of hyperglycemia after carbohydrate, no general conclusions can be drawn from this single experiment.

B. Protein Metabolism.—As already described under Case 1, a meal of bacon and eggs, eaten when glycosuria was absent, following the glucose tolerance test of December 12, brought about the elimination of 1 gm. sugar during the night. The experiments with beefsteak on January 16 and 17 showed that protein could give rise to slight glycuresis with or without elevation of the blood sugar. It is well known that phloridzin glycosuria is increased by protein feeding, and the sugar excretion is supposedly independent of the blood sugar level. The observations in Case 1 suggest some resemblance to the phloridzin process in this respect.

C. Carbohydrate Metabolism.—Certain salient features common to these three cases and to most or all of the genuine cases in the litera-

ture may be summarized as follows: (1) A tendency to glycosuria so strong that sugar freedom is possible only with stringent restriction of diet or actual fasting, to such a degree that health would be seriously impaired by attempting to keep glycosuria absent, if, indeed, life were possible at all — the cases in this respect surpassing true diabetes, except for very rare examples of extreme severity; (2) normal power of actual carbohydrate utilization, as manifested by "paradoxical tolerance"; i. e., though some process in the kidney or elsewhere causes the waste of a certain quantity of carbohydrate, and this quantity may increase with increased carbohydrate ingestion, yet the soundness of the fundamental assimilative function is shown by the ready utilization of the greater part of every starch or sugar intake, no matter how large; (3) though the blood sugar level is subject to some variations, the low values found in many cases even after large starch or sugar ingestion stand in contrast not only to the conditions in diabetes, but also to the hyperglycemia of normal persons after such feeding. The supposition that the kidneys here merely perform, more efficiently than in normal persons, the function of keeping the blood sugar concentration normal, encounters the following difficulties: First, the quantity excreted is often so small compared with the quantity ingested that the suppression of hyperglycemia through this drain alone seems questionable; second, the sugar curve does not necessarily correspond to the severity of the case or the intensity of the excretory process; the blood sugar may run low when the sugar loss is trivial, or higher when the excretion is considerable; third, there are other discrepancies, such as found in the protein test of Patient No. 1 on January 17. Here glycosuria was slight; not only did the kidneys fail to react so as to keep the blood sugar normal, but it was actually higher than should be expected in a normal person under the circumstances.

D. Total Metabolism. — There was some curiosity whether the sugar excretion was influenced only by the carbohydrate or by the total calories of the diet, but the observations on this point were very incomplete. No tests were performed with feeding of pure fat or alcohol. The details with various diets were mentioned in the description of Case 1. Patient No. 2, because of his nervous condition, was never subjected to fasting, but on a carbohydrate-free diet of 150 gm. protein and 800 calories the glycosuria fell to the vanishing point and possibly would have remained absent, the liberal protein alone failing to maintain the glycosuria. The only information from Case 3 is that glycosuria ceased very easily with fasting and returned with the feeding of only 25 gm. carbohydrate in green vegetables. It is a safe general conclusion that "renal glycosuria" is influenced chiefly by the pre-

formed carbohydrate and in smaller degree by the protein of the diet; but the evidence in Case 1 indicates, as far as it goes, that there is little or no influence of the total calories apart from these direct sources of carbohydrate.

Determinations of the respiratory metabolism may offer something of interest not only in general, but particularly in regard to the carbohydrate economy. They may show whether the rate of combustion of ingested carbohydrate is normal, and this again may throw some light on the rôle of mass action in assimilation. It seems to be a general law that when the concentration of any food substance is increased in the blood, both the combustion and the storage of that substance are increased, but there seem to be obstacles to considering the latter increase as caused by the former through simple mass action. Therefore, the possible demonstration of a rise of carbohydrate metabolism due to carbohydrate ingestion without the usual rise of blood sugar may be instructive, though there is an additional possibility that occult forms of carbohydrate in the blood may require consideration as well as the ordinary sugar.

6. CHARACTER OF THE SUBSTANCE EXCRETED

For convenience and brevity, the terms "glycosuria," "glucose" and "sugar" have been used with reference to the reducing substance in the urine, but are not intended for strict interpretation. In Case 2 the absence of fermentation with yeast created suspicion of pentosuria, which was excluded by the tests of Drs. Levene and Benedict. Subsequently, Benedict demonstrated that the reducing substance in this case was neither glucose nor any of the sugars heretofore reported in urine, but a new substance of yet unknown nature. In Cases 1 and 3 the reactions observed were typical for glucose, but in a strict sense glucose excretion was not positively demonstrated in these or in any cases in the literature. Case 2 may be exceptional, but the difficulty with fermentation in Case 1 on a few occasions suggests the possibility of transitions or close relations as respects the excreted substance. Absolute demonstration of glycosuria must consist of two parts; first, strict proof that the substance found in analysis is glucose; second, proof that this substance is present in urine obtained as fresh from the kidney as possible, and is not the product of changes occurring during standing or manipulation or even in the bladder.

7. NATURE OF THE CONDITION

Such scattering suggestions as the observations offered concerning the seat or nature of the anomaly are contained in the above summary. The hypothesis of E. Frank, that the apparently normal blood sugar

is due to impermeability of the corpuscles and the basis of glycosuria is a high level of sugar in the plasma, is here excluded because all the analyses were performed upon plasma. It had been planned to present a series of parallel plasma and whole blood analyses to show the permeability of the corpuscles, both for this reason and also as a matter of possible interest in comparison with the apparently increased permeability of the kidneys for sugar, but it was found at the end that the whole blood determinations had been invalidated by a slight technical error. The proportion of plasma and corpuscles as indicated by centrifugation in a graduated tube was followed as a routine in the laboratory; the results, being normal, are omitted, but as far as this method is concerned no connection was shown between this form of mellituria and the blood volume in Epstein's sense. A similarity to the phloridzin process is often suggested, but until something definite is learned concerning the actual mechanism in one or the other, the comparison of unknown with unknown must remain unproved and unprofitable. It is difficult to bring all cases in the literature under the same general rules, and uncertain whether they represent merely degrees and variations of one fundamental condition (confused sometimes with mild diabetes, or possibly sometimes complicated by it), or whether further study will reveal a group of independent anomalies. Benedict's recent investigation[2] includes one case which must be classified under the existing nomenclature as "alimentary renal glycosuria," provided it is not diabetes. The general information derived from Benedict's new methods is that all urine contains traces of carbohydrate in varying kinds and quantities, and that marked differences exist between individuals. The anomaly in question may prove to be only an unusual exaggeration of this normal process; it is conceivable that all gradations may be found between the strictest normality and the most extreme "renal glycosuria" with regard to the excretion of fermentable and unfermentable carbohydrate. Some facts, such as the peculiar blood sugar curves following carbohydrate or protein ingestion, do not fit easily with this supposition, but at present it promises nevertheless to be the most fruitful field for research.

SUMMARY AND CONCLUSIONS

1. The observation of three of these cases, as compared with thirty-seven cases of true diabetes in military service, and the increasing number of reports in the literature as blood sugar analyses are more employed, indicate that "renal" glycosuria is not as rare as once supposed, and probably is much commoner than other anomalies such as pentosuria or levulosuria.

2. J. Biol. Chem. **34**:195 (April) 1918.

2. The etiology, whether congenital or acquired, is unknown in two of these three cases. The history in one case is of special interest, as suggesting that severe trauma was either the primary or at least the exciting cause.

3. There was no indication of nephritis or renal abnormality in any of the three cases, except a slightly subnormal phenolsulphonephthalein elimination.

4. The apparent absence of harm in all three patients on unrestricted diet with continuous sugar excretion agrees with the favorable prognosis of this condition according to the literature. The only disturbance of health is that resulting from the severe restrictions of diet necessitated by any attempt to stop the sugar excretion. The sharp contrast with true diabetes in this respect is of theoretical as well as practical interest.

5. No fixed relations were observed between the sugar in blood and urine. The renal excretion does not necessarily serve to maintain a low level of blood sugar. The output is not always higher with high than with low blood sugar.

6. No fixed relations were observed between sugar and water elimination, in the sense either of polyuria due to glycosuria, or a flushing out of extra sugar by increased diuresis. More detailed studies of this and the preceding point would be desirable.

7. The sugar excretion seems to be determined by the supply of available carbohydrate, especially preformed, but also to less degree by the potential carbohydrate of protein. The fat ration and total metabolism, which are important in true diabetes, are probably without influence here.

8. Analyses of blood fat in one case showed abnormalities from which no conclusion can be drawn. No abnormal tendency to acidosis was observable in any of the three cases.

9. The excreted substance in one of the three cases seemed to be an unknown sugar, distinguished from glucose by the absence or incompleteness of fermentation. This may be the most important observation of the present study, and suggests the desirability of closer examination of the fresh urine in such cases for accurate identification of the sugar.

10. The nature of so-called "renal glycosuria" is not established. Frank's hypothesis of a high plasma sugar did not hold in these three cases. It is not yet proved that the abnormality lies in the kidney, or that it consists merely in a lowering of the normal threshold of sugar excretion. It is possible that cases differ in kind as well as degree, and that a group of anomalies have heretofore been included under this name.

A GROUP OF SIXTY-EIGHT CASES OF TYPE I PNEUMONIA OCCURRING IN THIRTY DAYS AT CAMP UPTON

WITH SPECIAL REFERENCE TO SERUM TREATMENT

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From February 10, to March 12, 1919, 135 cases of pneumonia were admitted to the Base Hospital; of this number, 50 per cent., or sixty-eight cases, were diagnosed bacteriologically as having type I pneumococcus the predominating organism in their infection.

This small epidemic was practically confined to colored troops, only four out of the sixty-eight cases affecting white men. These troops embarked from Brest, sailing to New York, and were then transferred to Camp Upton for demobilization.

On entering the hospital they presented the picture of acute lobar pneumonia. The classical signs were present in all, and only differed in the intensity of their symptoms. Starting with a chill — pain in the affected side, grunting respiration, with dilating alae nasi completed the picture of this type of disease. The early sputum was blood streaked; later it became prune juice in color. Dulness over the affected area became an early sign, and this was associated with bronchial and tubular breathing which increased with intensity as the dulness increased. The vocal fremitus was marked and we soon saw that we were dealing with acute lobar pneumonia.

There had been only eighteen cases of type I pneumonia during the influenza epidemic, and this group of cases was considered a fertile field for a thorough test of the type I serum as a method of treatment. Over 90 per cent. of these cases presented the picture of healthy seasoned troops, and it was with much interest that we watched the outcome of this method of treatment originated by the Rockefeller Institute and so admirably portrayed in their monograph dated October 16, 1917. We have used this method of treatment in our other cases of type I pneumonia, but they were not many and were distributed more or less irregularly throughout the different seasons of the year.

In the sputum typing of these cases, fifty-eight were straight type I, while ten were mixed; but with type I pneumococcus predominating, and were not different in any detail from the type ones.

In the table we have listed these cases by number, trying to arrange them as nearly as possible on the day and hour of their admission. Their date of embarkation and debarkation with the date of arrival and probable date of the onset of their sickness. The date of their arrival at the hospital, with the date of the typing of the sputum, corresponds to the date with the hour mentioned of the first injection of the serum. The table also shows the total amount of serum at eight-hour intervals given to each patient; the temperature, pulse and respiration on admission; the lobes of the lungs clinically involved, represented in numbers corresponding to number 1 the right upper; number 2, the right middle; number 3, the right lower; number 4, the left upper, and number 5, the left lower. A blood count was taken in nearly all of the cases and evidenced a marked leukocytosis with a high polymorphonuclear count, which is characteristic in this condition. The urine showed albumin and casts. In the majority of cases, 1 plus, corresponding to a trace, up to 3 plus, which is a marked amount. The casts are recorded in like manner, and these findings well represent the condition of the urine found in this type of pneumonia. The roentgen ray was used in checking up the clinical findings and the lobes involved are also represented numerically. Blood cultures were taken as indicated. We have tried to classify the recovered cases under the headings of crisis and lysis, and we have used in our distinction for crisis any temperature which drops to normal within thirty-six hours. The disposition of the case is determined by either duty or death, with the date corresponding in each column. Under remarks we have mentioned the principal complications which were characteristic of this group of cases, or we call attention to any abnormality which arose. The necropsy remarks are limited to the chest findings with the exception of two cases, one associated with pericarditis with effusion and the other with meningitis.

On admission to the pneumonia wards the physical examination was at once made, and if lobar pneumonia was present or suspected the patient received ½ c.c. of normal horse serum subcutaneously for desensitizing purposes; at the same time, the sputum was sent to the laboratory for typing. This method saved about five hours, the time which must elapse after giving the horse serum before the antipneumococcic serum may be administered. During this time, while waiting for the typing to return, a blood count is made and in many cases a blood culture is taken. The urine was sent for examination and a roentgen-ray examination was ordered to check the physical findings.

Within from four to six hours after the patient's admission to the hospital he is ready to receive his first injection, and we have obtained enough physical and laboratory data for accurate interpretation, before any change which might take place after the administration of the first dose of serum. We were also able to satisfy ourselves that after giving the first injection, there was little change in the blood picture. For example, we found that a differential count made before and shortly after the serum was administered remains the same. Only three cases of slight anaphylaxis occurred; a few had a thermal reaction immediately following the injection, similar in character to the reaction following the injection of a foreign protein intravenously, this being followed by a chill, elevation of temperature and sweating. This reaction has always been a favorable one in our experience and several times has resulted in prompt recovery by crisis. The serum sickness came on in practically all of the cases in from four to sixteen days after the last injection, the greatest discomfort being from the urticaria and occasionally from asthma. These symptoms were readily relieved by a hypodermic injection of from ½ to 1 c.c. of epinephrin in a 1:1,000 solution. The serum was given at eight-hour intervals, day and night, until the rectal temperature registered 100 or lower, or evidence of complications of impending death made it advisable to stop the treatment.

The dosage employed was 100 c.c. given intravenously, keeping the serum slightly warmer than the body temperature and allowing it to flow in very slowly. A gravity bottle was used, this being connected with an intravenous needle by rubber tubing around which were wrapped warm towels, to keep the solution at the proper temperature. A feeling of warmth was mentioned by many of the patients and sweating was common during the administration. Many of them complained of itching over different parts of the body and a few had manifest symptoms of urticaria, and it was the marked exception for an attack of asthma to come on during the administration of the initial dose. We have used any one of the three different preparations of the serum we have had in stock and frequently patients would, during their course of treatment, have serum from all three kinds. We have demonstrated to our own satsfaction that the serum does no harm.

Sixty-one of the sixty-eight patients received the serum; the least amount given to any one individual was 30 c.c., the largest amount, 900 c.c. The total amount used was 20,955 c.c., or the average amount per patient of 344 c.c. Of the seven not receiving serum, six were in convalescence when typed and one received no serum because of the diagnosis of type 4 pneumococcus and *Bacillus influenzae* in the sputum, but at necropsy this case showed a pure culture of type I pneumococcus from the heart's blood.

CONDENSED REPORT OF THE FINDINGS OF—

Case No.	Date of Embarkation	Date of Debarkation	Date of Arrival at Upton	Date of Onset of Disease	Date of Admission to Hospital	Date of Typing of Sputum	Hour of First Serum Injection	Total Amount Given, C.c.	On Admission			Lobes Involved 1-2-3-4-5 Number of Lobe	Blood Count	
									Temperature	Pulse	Respiration		W.B.C.	Poly.
1	2/ 2/19	2/10/19	2/10/19	2/ 7/19	2/10/19	2/11/19	10:30 p.m.	300	102.2	136	36	3	28,600	94
2	2/ 2/19	2/10/19	2/10/19	2/ 6/19	2/10/19	2/11/19	11:00 a.m.	300	105.4	124	30	4-5	21,600	82
3	2/ 2/19	2/10/19	2/10/19	2/ 9/19	2/10/19	2/11/19	10:00 p.m.	500	105.2	104	28	2-3	15,600	86
4	2/ 1/19	2/ 9/19	2/10/19	2/11/19	2/12/19	2/16/19	2:15 p.m.	500	103.2	88	22	5	12,200	79
5	2/ 4/19	2/12/19	2/12/19	2/ 8/19	2/12/19	2/13/19	8:30 p.m.	300	102.4	112	46	5	42,200	91
6	2/ 1/19	2/ 9/19	2/10/19	2/ 9/19	2/12/19	2/13/19	12:30 p.m.	30	100	80	20	4	.....	..
7	2/ 4/19	2/12/19	2/12/19	2/ 8/19	2/12/19	2/13/19	.....	...	101.6	96	22	2	13,400	75
8	2/ 2/19	2/10/19	2/10/19	2/12/19	2/13/19	2/13/19	1:30 p.m.	100	101.6	112	36	1-2	27,000	80
9	2/ 1/19	2/ 9/19	2/10/19	2/ 9/19	2/13/19	2/16/19	3:00 p.m.	100	103.2	100	24	1 3	6,600	71
10	Camp organization			2/12/19	2/13/19	2/21/19	10:30 a.m.	100	102	100	28	3 5	5,400	58
11	2/ 1/19	2/ 9/19	2/10/19	2/10/19	2/14/19	2/16/19	8:30 p.m.	100	102	120	28	3	17,600	90
12	2/ 4/19	2/12/19	2/12/19	2/13/19	2/15/19	2/17/19	8:00 p.m.	200	105.2	114	32	4-5	25,600	81
13	2/ 4/19	2/12/19	2/12/19	?	2/15/19	2/16/19	12:00 a.m.	200	103	110	40	1-2-3	20,100	83
14	2/ 2/19	2/10/19	2/10/19	2/12/19	2/16/19	2/18/19	8:00 p.m.	200	101.4	104	36	1-2-3	20,100	83
15	2/ 3/19	2/11/19	2/12/19	2/16/19	2/16/19	2/18/19	8:00 p.m.	400	104	118	28	5	27,300	80
16	2/ 3/19	2/11/19	2/12/19	2/17/19	2/17/19	2/18/19	10:30 p.m.	400	103.2	108	24	5	25,000	80
17	2/ 1/19	2/ 9/19	2/10/19	2/16/19	2/17/19	2/19/19	10:30 p.m.	185	103.8	120	30	1-2	28,000	85
18	2/ 2/19	2/10/19	2/10/19	2/17/19	2/18/19	2/23/19	10:00 p.m.	600	101	96	22	1	.....	..
19	2/ 4/19	2/12/19	2/12/19	2/18/19	2/19/19	2/24/19	12:00 a.m.	500	98	100	18	4-5	.....	..
20	2/ 3/19	2/11/19	2/12/19	2/ 8/19	2/16/19	2/18/19	.....	...	100	112	28	1 3	.....	..
21	Camp organization			2/20/19	2/21/19	2/23/19	.....	...	103	115	30	5	.....	..
22	2/ 2/19	2/10/19	2/10/19	2/21/19	2/22/19	2/24/19	12:00 a.m.	400	104	120	24	4-5	27,500	?
23	2/16/19	2/24/19	2/24/19	2/25/19	2/26/19	2/27/19	8:00 p.m.	200	103.4	120	36	5	.....	..
24	2/16/19	2/24/19	2/24/19	2/16/19	2/28/19	3/ 1/19	11:30 p.m.	300	102	100	28	1-2-3	.....	..
25	2/16/19	2/24/19	2/24/19	2/27/19	3/ 3/19	3/ 4/19	.....	...	105.6	112	22	5	.....	..
26	2/23/19	3/ 1/19	3/ 2/19	3/ 3/19	3/ 4/19	3/ 6/19	4:00 p.m.	100	105.8	126	46	3	.....	..
27	2/23/19	3/ 1/19	3/ 2/19	2/25/19	3/ 5/19	3/ 6/19	8:00 p.m.	400	102	108	36	1-2	17,000	78
28	2/ 3/19	2/11/19	2/11/19	2/10/19	2/11/19	2/13/19	7:30 p.m.	100	102.8	102	24	1-2-3-4	16,700	..
29	2/ 2/19	2/10/19	2/10/19	2/11/19	2/12/19	2/13/19	8:15 p.m.	385	105	126	36	5	50,000	23
30	2/ 1/19	2/ 9/19	2/10/19	2/12/19	2/14/19	2/16/19	8:00 p.m.	200	103.3	118	36	5	18,200	86
31	2/10/19	2/10/19	2/10/19	2/12/19	2/15/19	2/18/19	11:20 p.m.	100	104	120	30	1	21,000	87
32	2/ 3/19	2/11/19	2/12/19	2/ 9/19	2/16/19	2/18/19	8:00 p.m.	500	103.8	120	30	3	28,000	85
33	2/ 3/19	2/11/19	2/12/19	2/16/19	2/17/19	2/18/19	11:00 p.m.	400	104.4	118	30	1	21,600	91
34	2/ 2/19	2/10/19	2/10/19	2/14/19	2/18/19	2/21/19	4:15 p.m.	200	104.6	116	34	2-3	7,700	..
35	2/ 2/19	2/10/19	2/10/19	2/15/19	2/19/19	2/21/19	8:00 a.m.	200	101.8	92	26	5	9,600	61
36	2/16/19	2/24/19	2/24/19	2/23/19	2/27/19	3/ 3/19	2:00 p.m.	400	103	100	40	3	.....	..
37	2/16/19	2/24/19	2/24/19	2/25/19	2/27/19	2/28/19	12:00 p.m.	400	104	104	36	3	.....	..
38	2/20/19	2/28/19	2/28/19	2/28/19	2/28/19	3/ 3/19	10:30 p.m.	400	103	106	24	5	.....	..

—Sixty-Eight Cases of Type I Pneumonia

Urine		Roentgen-Ray Findings Lobes 1-2-3-4-5 Number of Lobe	Blood Culture	Date of		Date of		Remarks: Complications and Necropsy Findings
Albumin	Casts			Crisis	Lysis	Duty	Death	
2 plus	Neg.	1-2	Not taken	Temp. 103.6 at death		.....	2/15/19	Marked delirium throughout, marked toxemia Necropsy—Right pleural cavity, 100 c.c. turbid fluid; fibrinous exudate on surface of 1 and 2; 1, 2, 3 gray hepitization
2 plus	Neg.	5 fluid left base	.....	Temp. 99.6 at death		.....	2/18/19	Marked delirium throughout, marked toxemia Necropsy—Lobes 4, 5 covered with yellow exudate, consol. throughout containing no air; 1, 2, 3 bronchopneumonia
1 plus	Neg.	2-3	.....	.....	2/12 to 2/17/19	3/12/19	.....	None
Neg.	Neg.	.....	.....	.....	2/15 to 2/19/19	3/14/19	.....	None
2 plus	2 plus	4-5 fluid left base	.....	Temp. 99.2 at death		.....	3/10/19	Empyema, acute pericarditis Necropsy—Left pleura, 1,000 c.c. thick yellow pus; acute pericarditis; 500 c.c. of turbid fluid in pericardium
Neg.	Neg.	.....	.....	2/14/19	.....	2/27/19	.....	Anaphylaxis
1 plus	Neg.	.....	.....	2/13/19	.....	2/27/19	.....	Temperature never over 100.2
1 plus	Neg.	.....	.....	2/15/19	.....	3/ 1/19	.....	Atypical crisis
1 plus	Neg.	.....	.....	2/15/19	.....	3/ 4/19	.....	Leukocyte count after normal temperature
1 plus	Neg.	.....	.....	2/23/19	.....	3/12/19	.....	Leukocyte count after normal temperature
1 plus	Neg.	3-thickened pleura rt. base	.....	2/16/19	.....	3/18/19	.....	Atypical crisis
Neg.	Neg.	.....	Sterile	Temp. 103 at death		.....	2/19/19	Marked toxemia, beginning empyema rt. side Necropsy—Lobes 4 and 5, fibrinous exudate, firmly consolidated throughout
1 plus	Neg.	.....	Positive for Type I	Temp. 103.6 at death		.....	2/19/19	Admitted in convulsions Type I pn. meningitis Necropsy—1, 2, 3 firmly consolidated; meningitis Type I pneumococcus
2 plus	Neg.	.....	Sterile	2/18/19	.....	3/ 2/19	.....	
1 plus	Neg.	Sterile	.....	2/17/19	.....	3/12/19	.....	Pseudo crisis and post-critical rise, 12 hours
1 plus	Neg.	.....	.....	2/19/19	.....	3/12/19	.....	Ending by crisis on second day, serum sickness marked
1 plus	Neg.	1-2	.....	.....	2/17 to 3/22/19	3/ 4/19	.....	
Neg.	Neg.	1-2	.....	2/24/19	.....	3/14/19	.....	Atypical crisis
1 plus	1 plus	4-5 thickened pleura and fluid	.....	.....	2/24 to 2/26/19	3/14/19	.....	
Neg.	Neg.	.....	.....	2/18/19	.....	3/ 6/19	.....	Crisis on same day as typing, no serum
Neg.	Neg.	.....	.....	.....	2/21 to 2/24/19	3/14/19	.....	Lysis began on day of admission
1 plus	1 plus	4-5 thickened pleura	.....	2/28/19	.....	3/14/19	.....	Pseudo crisis followed by crisis
Neg.	Neg.	.....	.....	3/ 2/19	.....	3/14/19	.....	
Neg.	Neg.	1-2-3	.....	.....	3/2 to 3/ 5/19	3/21/19	.....	
1 plus	1 plus	.....	.....	3/ 5/19	.....	3/21/19	.....	Crisis occurred on day of admission, no serum
1 plus	1 plus	.....	.....	3/ 6/19	.....	4/15/19	.....	Single dose of serum given during crisis
1 plus	1 plus	1-2	.....	.....	3/6 to 3/10/19	3/14/19	.....	Secondary rise of temperature not due to serum sickness
Neg.	Neg.	1-2-3-4	.....	.....	2/15 to 2/17/19	4/15/19	.....	Delayed resolution with irregular temperature
1 plus	2 plus	5 fluid at base	.....	2/15/19	.....	2/17/19 4/ 1/19	.....	Serum reaction severe
Neg.	Neg.	Lungs neg. for fluid	Sterile	2/18/19	.....	3/22/19	.....	
Neg.	Neg.	2-3	Sterile	.....	2/17 to 2/22/19	3/21/19	.....	Cause undetermined, prolonged lysis
Neg.	Neg.	1-2	.....	.....	2/20 to 2/26/19	4/ 5/19	.....	
Neg.	Neg.	1	.....	2/28/19	.....	3/19/19	.....	Moderate jaundice, delayed resolution
2 plus	2 plus	1-2	Sterile	.....	3/4 to 3/7/19	3/22/19	.....	
1 plus	1 plus	5	.....	2/21/19	.....	4/ 5/19	.....	Delayed crisis
Neg.	Neg.	2-3	.....	3/ 4/19	.....	3/21/19	.....	Negative
1 plus	2 plus	2	.....	.....	3/2 to 3/5/19	3/28/19	.....	Delirium
1 plus	1 plus	.....	.....	3/ 4/19	.....	3/21/19	.....	

CONDENSED REPORT OF THE FINDINGS OF SIXTY-EIGHT—

Case No.	Date of Embarkation	Date of Debarkation	Date of Arrival at Upton	Date of Onset of Disease	Date of Admission to Hospital	Date of Typing of Sputum	Hour of First Serum Injection	Total Amount Given, C.c.	On Admission			Lobes Involved 1-2-3-4-5 Number of Lobe	Blood Count	
									Temperature	Pulse	Respiration		W.B.C.	Poly.
39	2/16/19	2/24/19	2/24/19	2/24/19	2/26/19	2/28/19	8:15 p.m.	250	105.2	112	32	1-2	.....	..
40	2/20/19	2/28/19	2/28/19	3/ 6/19	3/ 8/19	3/ 9/19	10:00 p.m.	300	100	90	22	1-2	7,000	62
41	2/25/19	3/ 5/19	3/ 6/19	3/ 7/19	3/ 8/19	3/ 9/19	10:00 a.m.	500	102.4	100	20	3	8,000	52
42	2/23/19	3/ 1/19	3/ 2/19	3/ 1/19	3/ 2/19	3/ 4/19	12:00 p.m.	300	102	110	20	4-5	.....	..
43	2/26/19	3/ 6/19	3/ 6/19	3/ 2/19	3/ 6/19	3/ 7/19	12:00 p.m.	300	105.2	118	30	4	16,000	77
44	2/23/19	3/ 1/19	3/ 1/19	3/ 3/19	3/ 5/19	3/ 7/19	12:00 p.m.	100	101	114	32	5	.....	..
45	2/23/19	3/ 1/19	3/ 1/19	3/ 6/19	3/ 6/19	3/ 8/19	12:15 p.m.	600	104.4	110	24	1	13,400	82
46	2/23/19	3/ 1/19	3/ 1/19	3/ 6/19	3/ 6/19	3/ 6/19	12:00 p.m.	500	102.4	118	42	1	.....	..
47	2/23/19	3/ 1/19	2/ 1/19	3/ 2 19	3/ 2 19	3/ 5/19	4:00 p.m.	700	102.8	100	26	4	9,800	80
48	2/23/19	3/ 1/19	3/ 1/19	2/26/19	3/ 9/19	3/12/19	12:30 p.m.	100	100.6	90	24	.....	12,400	84
49	2/23/19	3/ 1/19	3/ 1/19	3/ 2/19	3/ 7/19	3/ 8/19	5:00 a.m.	500	102.6	108	32	2	14,400	75
50	Camp organization			3/11/19	3/12/19	3/13/19	11:30 a.m.	400	105.4	114	22	2-3	9,600	80
51	Camp organization			3/11/19	3/ 5/19	3/14/19	4:00 p.m.	125	100	98	20	5	7,800	74
52	2/23/19	3/ 1/19	3/ 1/19	2/22/19	3/ 5/19	3/ 7/19	5:00 p.m.	300	99.4	104	22	5	33,200	85
53	2/23/19	3/ 1/19	3/ 1/19	3/ 8/19	3/10/19	3/12/19	12:15 a.m.	400	105	138	48	2	8,000	63
54	2/23/19	3/ 1/19	3/ 1/19	3/ 6/19	3/ 9/19	3/12/19	.....	...	101.4	124	22	5	.....	..
55	2/23/19	3/ 1/19	3/ 1/19	2/22/19	3/ 2/19	3/ 4/19	8:30 p.m.	600	103.2	102	22	1-2-3	13,200	85
56	2/16/19	2/24/19	2/24/19	2/26/19	2/27/19	2/27/19	8:30 p.m.	700	104.4	110	24	1-2-3	11,400	71
57	2/23/19	3/ 1/19	2/ 1/19	2/28/19	3/ 5/19	3/ 6/19	4:00 p.m.	900	104.4	124	24	4	28,600	91
58	2/23/19	3/ 1/19	3/ 1/19	2/22/19	2/26/19	2/27/19	4:00 p.m.	300	103	104	32	1	.....	..
59	Camp organization			3/ 7/19	3/ 8/19	3/ 9/19	10:00 a.m.	780	105	120	36	1	50,200	96
60	2/23/19	3/ 1/19	3/ 1/19	2/22/19	3/ 3/19	3/ 5/19	8:00 p.m.	600	102.2	128	28	4-5	.....	..
61	2/23/19	3/ 1/19	3/ 1/19	2/25/19	3/ 3/19	3/ 4/19	8:00 p.m.	400	103.8	110	38	3 5	.....	..
62	2/ 3/19	2/11/19	2/12/19	2/15/19	2/16/19	2/17/19	10:00 p.m.	200	100	84	20	4-5	19,600	87
63	2/16/19	2/24/19	2/24/19	2/25/19	3/ 2/19	3/ 3/19	.....	...	103.2	94	28	3	.....	..
64	Camp organization			3/ 6/19	3/ 7/19	3/ 7/19	12:00 p.m.	200	103	110	26	3	29,200	91
65	Camp organization			2/20/19	2/20/19	2/22/19	10:30 p.m.	300	103.6	120	24	4-5	24,000	89
66	2/23/19	3/ 1/19	3/ 1/19	3/ 1/19	3/ 2/19	3/ 4/19	8:00 p.m.	700	101.4	96	24	5	.....	..
67	2/23/19	3/ 1/19	3/ 1/19	2/28/19	3/ 3/19	3/ 5/19	4:00 p.m.	200	101.4	76	20	4-5	.....	..
68	2/23/19	3/ 1/19	3/ 1/19	3/ 1/19	3/ 4/19	3/ 7/19	.....	...	101.3	96	28	1-2-3 5	26,800	83

—CASES OF TYPE I PNEUMONIA—(*Continued*)

Urine		Roentgen-Ray Findings Lobes 1-2-3-4-5 Number of Lobe	Blood Culture	Date of		Date of		Remarks: Complications and Necropsy Findings
Albumin	Casts			Crisis	Lysis	Duty	Death	
1 plus	2 plus	1-2	.....	2/30/19	.....	3/22/19	.....	Delirium
Neg.	Neg.	1-2	.....	3/10/19	.....	3/25/19	.....	Leukocyte count after crisis
1 plus	1 plus	2-3 partial of 1	.....	3/11/19	.....	3/25/19	.....	Leukocyte count 1 week after crisis
1 plus	1 plus	1- 4-5	.....	3/ 5/19	.....	3/25/19	.....	
1 plus	1 plus	Broncho 4-5	.....	.....	3/8 to 3/12/19	4/ 5/19	.....	
1 plus	3 plus	.....	.....	3/ 9/19	.....	4/ 5/19	.....	Atypical crisis followed by irregular temp.
1 plus	Neg.	1	.....	3/ 9/19	.....	3/26/19	.....	
1 plus	Neg.	.....	.....	.....	3/8 to 3/10/19	3/26/18	.....	
1 plus	Neg.	4-5	.....	.....	3/6 to 3/10/19	4/ 1/19	.....	
Neg.	Neg.	2	.....	.....	3/10 to 3/14/19	3/29/19	.....	Admitted in convalescence
1 plus	2 plus	2-2	.....	3/ 9/19	.....	3/29/19	.....	
Neg.	Neg.	2-3	.....	.....	3/12 to 3/16/19	4/15/19	.....	Serum reaction marked
1 plus	1 plus	5	.....	.....	3/14 to 3/15/19	4/ 5/19	.....	Serum reaction marked
1 plus	1 plus	Lungs neg. for fluid	.....	3/ 8/19	.....	4/15/19	.....	
Neg.	Neg.	1	.....	3/13/19	.....	4/ 5/19	.....	Atypical crisis
Neg.	Neg.	.....	.....	3/10/19	.....	4/15/19	.....	No serum, temperature dropped from 105 to 98.6 in 16 6hours
1 plus	3 plus	1-2-3 -5	.....	.....	3/6 to 3/9/19	4/29/19	.....	Serum reaction marked, delayed resolution
1 plus	2 plus	1-2-3 fluid at base	.....	.....	3/2 to ?	5/27/19	.....	Sterile fluid at right base, delayed resolution
1 plus	2 plus	5 and base of 4	Sterile	.....	3/9 to 3/11/19	4/ 5/19	.....	Meningismus, spinal fluid negative; serum reaction marked
1 plus	2 plus	.....	.....	2/28/19	.....	3/12/19	.....	
Neg.	Neg.	1-2	Sterile	Temp. 99.6 at death		.....	3/23/19	Otitis media Type I, also K. L. found in throat and ear Necropsy—Lobe 1 consol., fibrin. exudate; 2, 3, 4, 5 bronchopneumonia; mastoiditis rt. pn. Type I; meninges negative
3 plus	1 plus	.....	.....	Temp. 102.8 at death		.....	3/ 9/19	Marked toxemia Necropsy—Lobes 4 and 5 consol.; covered with fibrinous exudate
Neg.	Neg.	.....	.....	Temp. 97.4 at death		.....	3/ 9/19	Marked toxemia Necropsy—Lobe 3 bluish red, solid throughout; 20 c.c. bloody fluid in pleural cavity; lobe 5 solid throughout
1 plus	1 plus	.....	.....	3/18/19	.....	3/ 4/19	.....	
1 plus	3 plus	.....	.....	3/ 3/19	.....	3/18/19	.....	Crisis before typing returned
Neg.	Neg.	3	.....	3/ 8/19	.....	3/18/19	.....	Crisis before typed
Neg.	Neg.	4-5 thickened pleura fluid base	.....	.....	2/21 to 2/23/19	5/12/19	.....	Empyema left, Type I isolated
1 plus	1 plus	4-5 fluid at base	.....	.....	3/6 to ?	5/13/19	.....	Empyema left, Type I
1 plus	1 plus	.....	.....	Temp. 100 at death		.....	3/11/19	Abscess of left upper lobe with cavity Necropsy—Lobes 4 and 5 consol. and multiple abscesses throughout; pneumonia and tuberculosis present
1 plus	1 plus	1-2-3	.....	Temp. 106.4 at death		.....	3/17/19	Entered hospital during convalescence Necropsy—Lobe 3 consol.; all lobes involved; much yellow exudate both chests

Of the sixty-one patients having the serum, thirty recovered by crisis, twenty-two by lysis and nine died. To the thirty who recovered by crisis a total amount of 8,665 c.c. was administered or an average dose of 288 c.c. Those ending in lysis received a total amount of 9,010 c.c., or an average dose per individual of 410 c.c. To those who died 3,200 c.c. were given, or an average dose per individual of 356 c.c.

In addition to the serum treatment, the general treatment was carried out. Each patient had 1,000 cu. ft. of air space. The windows were open day and night, and on sunny days the patients were moved to the porch. Rather large doses of digitalis and whisky were used during the critical stage, and codein was administered when a sedative was necessary.

The Rockefeller Institute states that the expected rate of mortality in this type of pneumonia where the serum is not used is 25 per cent. Their mortality rate with the use of the serum, in a series of 101 cases, was 7.5 per cent., using an average amount per individual of 250 c.c. Our mortality rate was 14.7 per cent. This higher death rate might be explained by a lower resistance to pneumonia in the colored race, the unfavorable season of the year and the forced moving of troops from place to place. Miller and Lusk in their report on pneumonia at Camp Dodge state that among sixty-nine cases of type I pneumonia, occurring in six months, in which no serum was used, the mortality rate was 2.8 per cent. We regret that we did not divide this series of cases into two groups, giving one half serum and the other half none.

We feel that this epidemic of type I pneumonia was caused by the close association of the men on the transports after being exposed to the inclement weather of Brest, as most of the cases developed on the boats or soon after landing.

We have used the type I serum in two cases of pneumonia with positive blood cultures, one with *Streptococcus viridans* and the other type IV pneumococcus. Each patient received eight injections after which the blood cultures of both were sterile and both recovered. This was done in desperation because of the death of three patients with positive blood cultures developing prior to these two.

THE DETERMINATION OF HEMOGLOBIN BY THE ACID HEMATIN METHOD

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In the course of a study of the blood in the anemias of infancy, certain discrepancies were encountered in the acid hematin method of determination of hemoglobin described by Sahli.[1] The study of the cause of these discrepancies has led to a modification of the method to produce accurate determinations comparable with those obtainable when a determination of hemoglobin by measuring its iron content, or by the carbon monoxid hemoglobin method, is made. These modifications consist in: first, the use of N/10 hydrochloric acid as the diluent of the acid hematin instead of water; and second, the employment of heat to bring the reaction of formation of the acid hematin to its endpoint of equilibrium more quickly than it occurs in the cold.

Since the introduction of the acid hematin method by Sahli, various criticisms of it have been made. From the mechanical side these have been well summed up by Kuttner[2] as inaccuracies due to variations in the calibration and construction of the tubes, the fading of the standard and the variations in blood volume depending on the time when the blood is taken for examination. There are, in addition to these mechanical sources of error, certain chemical conditions of inaccuracy in the determination. These do not seem to have been considered at all in most of the literature concerned with the hemoglobin content of the blood in health and disease. These are: First, variation in the hydrogen ion concentration of the final fluid obtained; and second, the effect of time on the amount of acid hematin formed. Disregard of these factors, which are closely dependent, is why two observers will often disagree about a hemoglobin determination made upon the same individual by the Sahli method.

As regards the factor of variation in the hydrogen ion concentration, Sahli stipulated that acid should not be added beyond the 10 mark on the calibrated tube. As shown by Stäubli,[3] however, the addition of acid up to the 12 mark, alone, results in an appreciable variation in the reading. This can be seen in Table 1. Now, it is obvious that it is difficult in ordinary clinical work, and working with ordinary clinical instruments, not to pass a trifle beyond the 10 mark. Progres-

1. Sahli: Lehrbuch d. Klin. Untersuch Methode, 1909, Ed. 5, p. 846.
2. Kuttner: J. A. M. A. **66**:1370 (April 29) 1916.
3. Stäubli: München. med. Wchnschr. **58**:2429, 1911.

sive increase in the hydrogen ion content, by adding more and more acid produces corresponding variations. By using N/10 HCl throughout a determination, one can eliminate this source of error.

TABLE 1.—Variation of Hemoglobin Reading with Concentration of Acid and Time

Acid Mark	One Minute Reading, Per Cent.	Twenty Minute Reading, Per Cent.
10	70	70
13	70	80
15	75	90
18	80	95
20	85	100
22	90	110

When N/10 HCl is used throughout a determination, a progressive increase in the darkening of the fluid, that is a progressive increase in the amount of acid hematin formed, occurs. This does not occur with the method of Sahli when only normal values are under consideration. But as noticed by Stäubli, with lower values, that is, those which occur in clinical work, a distinct change in the darkening occurs from the first minute until the end of twenty to forty minutes, so that a final reading should not be made until it has been found that the color remains constant. Meyer and Butterfield[4] have also mentioned this variation in the color of acid hematin until equilibrium is established. Recently Newcomer[5] studied the absorption spectra of acid hematin and showed that the rate of formation of acid hematin is a rectangular hyperbola of the form $xy = -c$, and that an approximate equilibrium is not established until the lapse of from twenty to forty minutes. This is illustrated in Table 2.

TABLE 2.—Variation of Hemoglobin Reading with Time (Hydrogen Ion Concentration Constant [10 Mark], Determination Carried Out Strictly According to the Directions of Sahli)

One Minute, Per Cent.	Ten Minutes, Per Cent.	Twenty Minutes, Per Cent.	Forty Minutes, Per Cent.
60	75	80	80
50	70	85	85
45	60	65	65
55	70	70	70
60	75	80	80
45	60	65	65
70	75	75	75
65	75	80	80
30	50	55	60
40	60	70	70

To wait twenty minutes in clinical work is relatively a long time. As the time interval is apparently consumed in bringing the reaction

4. Meyer and Butterfield: Arch. Int. Med. **14**:94 (July) 1914.
5. Newcomer: J. Biol. Chem. **37**:465 (March) 1919.

of formation of the acid hematin to its end point, the effect of heat in hastening it was studied. It was found that boiling for one minute over a free flame, after a reading made at the end of one minute, using N/10 hydrochloric acid as a diluent throughout, and then making a reading at the end of another minute, gave a reading equal to the one obtainable after waiting for twenty minutes at room temperature. The deeper color obtained when N/10 HCl is used as a diluent makes a more accurate comparison possible according to a general principle of colorimetry.

Determinations of the absolute hemoglobin based on the iron content by the author's method[6] gave readings corresponding to those calculated on the basis of the final reading. This is shown in Table 3. Determinations of the hemoglobin by the carbon-monoxid hemoglobin method of Palmer[7] also showed close agreement. This is shown in Table 4.

TABLE 3.—HEMOGLOBIN DETERMINATIONS COMPARED WITH IRON CONTENT OF BLOOD

Reading At Room Temperature After Twenty Minutes, Per Cent.	Reading After Boiling for One Minute, Per Cent.	Hemoglobin Calculated from Iron Content, Per Cent.
95	95	93
90	90	90
105	105	106
80	80	78
95	95	96
100	100	100
70	70	72
60	60	58
90	90	91
55	55	57

TABLE 4.—HEMOGLOBIN DETERMINATION COMPARED WITH DETERMINATION BY PALMER METHOD

Acid Hematin Method, Per Cent.	Palmer Method, Per Cent.	Acid Hematin Method, Per Cent.	Palmer Method, Per Cent.
65	67	60	61
80	80	70	73
55	54	65	66
60	62	85	82
75	75	45	44

SUMMARY OF METHOD

To obtain a rapid, accurate determination of hemoglobin with clinical instruments, using the acid hematin method which requires the least amount of time, material and training, the following steps are gone through: The blood is obtained with a carefully calibrated pipette, preferably when the patient has not yet had the first meal of

6. Berman: J. Biol. Chem. **35**:231 (Aug.) 1918.
7. Palmer: J. Biol. Chem. **33**:119 (Jan.) 1918.

the day. It is diluted with N/10 HCl and a reading is made at the end of one minute. Then the fluid in the calibrated tube is carefully boiled over the free flame for one minute. After permitting to cool for one minute it is again diluted with N/10 HCl and a final reading made. A standard similarly constructed with a known normal blood should be used, and be made freshly daily, to avoid error due to fading.

CONCLUSIONS

1. The method of Sahli does not furnish accurate determinations of hemoglobin within from 15 to 20 per cent.

2. A method is described by which an accurate reading may be rapidly obtained with the ordinary clinical instrument.

I am indebted to Dr. Charles Gilmore Kerley of New York for much of the material on which this study has been based, and also to Dr. Donald Van Slyke of the Rockefeller Institute for helpful assistance.

A STUDY OF THE RENAL CONCENTRATION POWER FOR URIC ACID IN EARLY CHRONIC INTERSTITIAL NEPHRITIS

PRELIMINARY PAPER

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In 1916 Myers and Fine[1] published a series of cases showing an increase of blood uric acid in early chronic interstitial nephritis. In later cases of this disease they showed an increase of blood urea and creatinin. Subsequently, in 1919 the same authors[2] drew attention to the fact that uric acid, urea and creatinin pass through the renal membrane with different degrees of ease. The kidney concentrates uric acid approximately twenty times, while it concentrates urea and creatinin approximately eighty and one hundred times, respectively.

With the above work as a point of departure, we instituted a series of studies regarding the renal concentration power for uric acid in early chronic interstitial nephritis with the thought that the findings might be utilized for accurate results in the early diagnosis of that disease.

The scope of the work is naturally divided as follows:

1. A study of the renal concentration power for uric acid in early chronic interstitial nephritis.

2. A study of the renal concentration power for uric acid in the nonnephritic kidney.

3. A study of the renal concentration power for uric acid in cases showing indefinite clinical or urinary symptoms, in which a diagnosis of nephritis is not possible by present methods—the subsequent development of such cases to be observed carefully.

With this classification in view, we have studied a number of successive cases as they presented themselves to one of us and a preliminary report of the work is here presented.

STANDARDIZATION OF OBSERVATION

In estimating the blood content of uric acid, the prevalent practice is to obtain the blood specimen before breakfast, the patient having been for a certain period on a diet low in nucleo-proteids. Such procedure is obligatory in order to eliminate the variable blood content of uric acid due to diet. Only by such regulation has it been possible to obtain a certain uniformity of standard.

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1. Myers and Fine: Arch. Int. Med. **17**:570 (April) 1916.
2. Myers and Fine: J. Biol. Chem. **32**:239 (Feb.) 1919.

In the present work such restrictions, however, have been considered by us undesirable for the following reasons:

1. In our study the actual blood and urine contents of uric acid are not important, the renal concentration power, which is sought, being obtained merely by the relation of the urine uric acid to the blood uric acid.

2. Under restricted diet the body metabolism is reduced and the functionating power of the body organs lessened. In estimating the renal concentration power it is not desirable that the functioning of the kidneys be reduced by purely dietary factors.

3. In the series of cases referred to in the initial paragraph of this article, Myers and Fine show that in early nephritis the blood uric acid content is but little elevated so that the concentration power of the kidney, in such cases, approaches the normal. In studying such cases, therefore, the diet should be such that the concentration power of the kidney can be observed under conditions of more or less stress.

Since the fluid intake, in all probability, influences the renal concentration power, at least so far as separate voidings of urine are concerned, for uniformity of observation, such was standardized as approximately normal.

The patients under observation were, therefore, placed on the following diet and fluid intake for forty-eight hours previous to taking the blood and urine specimens. These were taken simultaneously between 11 and 12 a. m.

DIET

Eat exactly according to this diet, both as to the quantity and particular articles of diet.

ON ARISING:

Drink 16 ounces of water

BREAKFAST:	Calories	
4 tablespoonfuls of cream of wheat, hominy or oatmeal	100	
3 ounces of cream	150	
1 slice bread	100	
1 pat of butter, 1 by 1 by ¼ inches	100	
1 soft egg	100	
8 ounces of cocoa	240	
8 ounces of water		
Total calories for breakfast		790

NOON:		
8 ounces of puree of pea, bean or potato	200	
2 lamb chops	200	
1 baked potato	100	
1 pat of butter	100	
4 tablespoonfuls of junket	80	
1 slice of bread	100	
1 pat of butter	100	
8 ounces of water		
Total calories for noon meal		880

6 P. M.:		
1 slice bread	100	
1 slice roast beef	100	
6 tablespoonfuls of green vegetables, string beans, cauliflower, cabbage, etc.	100	
1 pat of butter	100	
8 ounces of water		
6 tablespoonfuls of rice pudding, corn starch or custard	300	
3 ounces of cream	150	
6 ounces of milk	120	
Total calories for evening meal		970
10 P. M.:		
8 ounces of cocoa	240	240
Total calories for all meals		2,880

On the day the test is made, void urine prior to meals only and retain urine after meals until the time test is taken.

TECHNIC

Quantitative Method for Blood Uric Acid.—The colorimeter used was that of Benedict and Bock.

The method employed was that of Folin and Denis as modified by Benedict and Hitchcock. The amount of blood used for each test was 10 c.c. The specimen was not oxalated, but was at once mixed with 50 c.c. of hundredth normal acetic acid and immediately placed on the water bath. Special care was taken to obtain a good coagulum over the water bath before the mixture was boiled over the free flame. In every instance the total filtrate for evaporation was kept between 125 and 150 c.c. After the addition of the silver-ammonia-magnesia mixture to the concentrated filtrate, care was taken to keep the specimen long enough in the icebox to obtain complete separation before centrifuging. In no instance was the icebox time less than thirty minutes. In case of doubt in accurately matching the colors, that reading was taken which when computed would give the lowest amount of uric acid. Since it is well known that by the above method about 90 per cent. of the blood uric acid is extracted, 10 per cent. of the amount computed was added to give the final figures for blood uric acid.

Quantitative Method for Urine Uric Acid.—The method employed was that of Benedict and Hitchcock. The same precautions were taken for obtaining complete separation in the icebox as mentioned under blood uric acid. In cases of doubt in accurately matching the colors, that reading was taken which when computed would give the lowest amount of uric acid.

The renal concentration power was computed by dividing the amount of urine uric acid by the amount of blood uric acid, and it

should be noted that from the preceding in every instance the highest concentration power possible for that case was thus recorded.

DISCUSSION

We have accepted 3 mg. per 100 c.c. as the high normal limit for blood uric acid.

It is interesting to note that so far as blood uric acid content in early chronic interstitial nephritis is concerned, our figures as shown by Group 1 are in accord with the findings of Myers and Fine, mentioned at the beginning of this article and also with the more recent work of Baumann, Hausmann, Davis and Stevens.[3] High figures for blood uric acid were obtained in 85.6 per cent. of our cases of nephritis. On the other hand, 40 per cent. of our cases of negative nephritis also gave high figures for blood uric acid. This would indicate that while high blood uric acid is an exceedingly common symptom of early chronic interstitial nephritis, it is by no means a specific one. Its availability for the early accurate diagnosis of that disease is, therefore, materially limited.

It is also important to notice that in early chronic interstitial nephritis the height of blood uric acid increase is not a guide to the degree of impairment of the renal concentration power. There is no direct relation between the amounts of blood uric acid and the concentration of figures. Thus in Group 1, Cases 7 and 13, which are among the highest in blood uric acid, show the better concentration figures, while Cases 8 and 11, which show the lowest and practically normal amounts for blood uric acid, give much worse concentration figures. On the other hand, Cases 4 and 14, which are high in blood uric acid, give exceedingly poor concentration figures, and Cases 1 and 12, in which blood uric acid is only slightly elevated, show very fair concentration figures. In early chronic interstitial nephritis, therefore, the degree of impairment of the renal concentration function is not accurately gaged by mere blood uric acid content.

It is of special importance to note that the nonnephritic kidney shows a condition which is the direct opposite of the foregoing. In the nonnephritic kidney there *is* a direct relation between the blood uric acid content and the concentration figure. From Group 2, with the exception of Case 5, it is seen that the higher the blood uric acid content, the lower the concentration figure, and the lower the blood uric acid, the higher the concentration figure. In the nonnephritic, therefore, it would seem that as the blood uric acid content rises, the renal concentration power falls, and as the blood uric acid content

3. Baumann, Hausmann, Davis and Stevens: Arch. Int. Med. **24**:70 (July) 1919.

TABLE 1.—GROUP 1. CASES OF POSITIVE CHRONIC INTERSTITIAL NEPHRITIS

No.	Name	Age	Blood Pressure	Cardiac Area Verified by Roentgenograms	Cardiac Murmur	Brachials	Headache	Vertigo	Vision	Eye Ground	Loss of Weight	Digestive Disturbances	Albumin	Casts	Blood Urie Acid, Mg. per 100 C.c.	Urine Urie Acid, Mg. per 100 C.c.	Renal Concentration
1.	A. W. A.	49	170	Increased	—	+	+	+	+	+	—	+	+	—	3.16	38.8	12.2
2.	G. W. B.	52	140	—	—	+	+	+	+	—	+	+	+	—	3.87	17.0	4.4
3.	J. B.	45	122	—	—	+	+	+	+	—	+	+	+	+	5.11	19.48	3.8
4.	A. W. B.	60	170	Increased	+	+	+	+	+	—	—	+	+	—	6.27	22.0	3.5
5.	C. C. B.	46	112	—	+	+	+	+	+	—	+	+	+	+	4.12	24.0	5.8
6.	J. F. H.	57	170	Increased	—	+	+	+	+	—	+	+	+	+	4.96	37.5	7.5
7.	M. H.	70	165	Increased	+	+	+	+	+	—	+	+	+	—	6.24	64.0	10.2
8.	R. J.	50	190	Increased	+	+	+	+	+	—	—	+	+	—	2.24	15.6	7.0
9.	J. M.	62	160	Increased	+	+	+	+	+	—	+	+	+	—	3.48	21.84	6.0
10.	M. V. A.	58	154	—	+	+	+	+	+	—	+	+	—	—	5.72	15.0	2.6
11.	M. B.	58	198	Increased	+	+	+	+	+	—	+	+	+	—	3.02	13.12	4.3
12.	H. H.	14	110	—	+	—	+	+	—	—	+	+	+	+	4.00	56.0	14.0
13.	W. H. D.	65	190	Increased	+	+	+	+	+	+	+	+	—	—	8.25	107.0	12.9
14.	C. P.	46	110	Increased	+	+	+	+	+	+	+	+	—	—	7.42	32.83	4.4

TABLE 2.—GROUP 2. CASES OF NEGATIVE NEPHRITIS

No.	Name	Age	Blood Pressure	Cardiac Area Verified by Roentgenograms	Cardiac Murmur	Brachials	Headache	Vertigo	Vision	Eye Ground	Loss of Weight	Digestive Disturbances	Albumin	Casts	Blood Urie Acid, Mg. per 100 C.c.	Urine Urie Acid, Mg. per 100 C.c.	Renal Concentration
1.	R. R. B.	31	120	—	—	—	+	—	—	—	—	+	—	—	2.06	53.7	26.1
2.	F. H.	28	108	—	—	—	—	—	—	—	+	+	—	—	4.58	93.5	20.4
3.	R. A. S.	40	120	—	—	—	+	—	—	—	+	—	—	—	1.50	54.0	36.0
4.	C. N. J.	46	114	Increased	+	+	+	—	—	—	+	—	—	—	2.44	50.0	20.5
5.	H. A. H.	53	140	—	—	—	—	—	—	—	—	—	—	—	2.42	59.5	24.6
6.	H. W. H.	52	143	—	—	—	—	—	—	—	—	—	—	—	5.20	104.0	20.0
7.	C. H.	25	125	—	—	—	—	—	—	—	—	—	—	—	4.63	103.7	22.4
8.	W. H.	20	120	—	—	—	—	—	—	—	—	—	—	—	1.85	59.9	32.4
9.	F. D.	30	130	—	—	—	—	—	—	—	—	—	—	—	2.60	65.2	25.1
10.	A. D.	35	135	—	—	—	—	—	—	—	—	—	—	—	4.75	101.1	21.3

TABLE 3.—GROUP 3. QUESTIONABLE CASES OF CHRONIC INTERSTITIAL NEPHRITIS

No.	Name	Age	Blood Pressure	Cardiac Area Verified by Roentgenograms	Cardiac Murmur	Brachials	Headache	Vertigo	Vision	Eye Ground	Loss of Weight	Digestive Disturbances	Albumin	Casts	Blood Urie Acid, Mg. per 100 C.c.	Urine Urie Acid, Mg. per 100 C.c.	Renal Concentration
1.	F. S. D.	32	90	—	—	—	+	—	—	—	—	+	+	+	1.76	12.5	7.1
2.	M. H.	33	118	—	—	—	+	—	—	—	—	+	+	+	2.66	18.0	6.7
3.	A. J.	23	140	+	+	—	+	+	+	—	—	+	+	—	4.00	51.0	12.7
4.	R. R. R.	59	140	+	+	—	+	+	+	—	—	+	+	—	3.61	66.5	18.4
5.	M. S.	33	130	—	—	—	+	+	+	—	—	+	+	—	4.02	44.4	11.0
6.	R. W.	38	140	+	+	—	+	+	+	—	—	+	+	—	3.36	38.0	11.0
7.	E. H. W.	39	122	+	+	—	+	+	+	—	—	+	+	—	4.1	66.0	16.1
8.	H. D. S.	55	175	+	+	—	+	+	+	—	—	+	+	—	2.64	37.5	14.2
9.	A. R.	43	125	+	+	—	+	+	+	—	+	+	+	+	3.92	47.1	12.0
10.	L. M.	49	155	—	—	—	+	—	—	—	+	+	—	+	6.96	107.0	15.3

falls the renal concentration power rises. We are now engaged in a series of studies in order to ascertain to what extent this characteristic may be utilized in differentiatng the nonnephritic from the nephritic kidney.

The perspective of the concentration figures is best obtained by a consideration of the cases in their clinical groups, as follows:

1. A group (No. 1) which shows clinical symptoms diagnostic of nephritis. These all show a concentration figure of 14 or below.

2. A group (No. 2) which shows no clinical symptoms suggestive or diagnostic of nephritis. These all show a concentration figure of 20 or above.

The divergence in concentration figures between these two groups (nephritics and nonnephritics) is definite and marked. Such figures give a clean-cut division which leaves no room for doubt. No such clean-cut division is afforded by the figures for the blood uric acid contents.

3. A group (No. 3) which shows clinical symptoms suggestive but not diagnostic of nephritis. These all show concentration figures below 18.4.

It is our belief that this group in reality belongs with the positive nephritics in Group 1, and that such belief will be verified by the further clinical observations of these cases. Such observations are now under way, together with the study of other cases both from a clinical and concentration standpoint.

A further study of the effects of treatment on the concentration figures of positive nephritics is being undertaken by us.

ROENTGENOGRAPHIC STUDIES IN GOUT*

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Certain bony changes are found in the roentgenogram which roentgenologists maintain are pathognomonic evidence of gout. Occasionally roentgenologists of this hospital have made the diagnosis of gout from the roentgen-ray findings in cases in which there were no clinical evidences of that disease. This led to the present investigation, the purpose of which was to establish the diagnostic value of such roentgenographic findings. The latter were first described as occurring in the roentgenogram of the phalanges in a case of gout by Huber[1] in 1896. His observations have been confirmed by several other writers. A report by Koehler[2] contains some excellent plates and diagrams of the roentgenographic findings considered as peculiar to gout. Drinberg[3] in a further contribution to the subject has collected the literature up to 1911. The best articles are those of Strangeways[4] and Jacobsohn.[5] All writers have agreed that the roentgenographic changes in the bones described by Huber are always the result of tophi, except Strangeways, who expresses no definite opinion. The changes have been found in the bones of wrists, hands, ankles and feet.

We have investigated (1) the roentgenographic findings in the bones of the wrists, hands, ankles and feet of gouty patients, and (2) the frequency of the so-called pathognomonic gouty bony changes in the same anatomic regions in cases of chronic arthritis which were clinically not gout. A detailed report of the roentgenographic findings in nine gouty cases is made. All these patients had tophi from which sodium urate crystals were obtained. One case which was clinically not gout is described for purposes of comparison. This case had been diagnosed gout by a former roentgenologist of the hospital.

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The so-called gouty changes in the roentgenograms of the bones are represented by discrete, circular or oval areas of decreased density; that is, areas of rarefaction (Figs. 1, 2, 3, 4). These areas form segments of a circle when they occur in the edges of the bones. The borders of the areas are more or less distinct and often are very sharply defined. In the following roentgen reports the areas are designated as "focal areas of decreased density." The phrase "proliferative changes" is used to describe lipping and spur formation at the margins of the articular surfaces of bones. "Atrophy" designates the appearance in the roentgenogram resulting from partial absorption of the lime salts from bones. "Destruction" is used to designate irregular areas in which it appears as though complete absorption of bone had occurred.

REPORT OF CASES

CASE 1 (Med. No. 5278).—W. H. K.; woman; white; aged 29 years.

Diagnosis: Chronic arthritis.

The patient's habits were good. She had had chronic polyarthritis with occasional fairly acute exacerbations for the previous two years. The joints never had been severely painful or tender. During the previous six months stiffness of the knees had prevented walking. Physical examination was negative, except for the joints. There was limitation of motion and crepitation in all joints of the extremities. The elbows, wrists, finger joints, knees and joints of both great toes were enlarged, principally as the result of thickening of the periarticular tissues. There were no tophi. Blood pressure was 110 mm. systolic and 75 mm. diastolic. Urine examinations were negative, except for a scant trace of albumin and a rare cast in one of the specimens. Phenolsulphonephthalein excretion was 65 per cent. in two hours. Uric acid was 1.5 mg. and nonprotein nitrogen 28 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

Roentgen Report (No. 7912).—Hands and wrists: The lower ends of the radii, ulnae, all the bones of both carpi, of both metacarpi and of all the phalanges show marked atrophy (Fig. 1). The radio-ulnar-carpal joint space of each wrist is narrowed. The articular surfaces of both radii and ulnae are irregular in outline and show slight proliferative changes. The joint spaces in both carpi are narrowed. The heads of the left second and of the right third metacarpal bones are irregularly semicircular in outline due to partial bony destruction. In the right hand the first, second, third and fifth and in the left hand the first and second metacarpophalangeal joint spaces are narrowed. With the exception of the terminal joints of each little finger all the interphalangeal joints are narrowed or obliterated. The first interphalangeal joints of the second, third and fifth fingers of the left hand, of the third and fifth fingers of the right hand, and the second interphalangeal joint of the third finger of this hand are obliterated and replaced by mottled areas of increased density. About these joints and about the bases of the proximal phalanges of both index fingers there are proliferative changes. The distal articular surfaces of the radii and ulnae present several more or less circular areas of decreased density from 1 to 3 mm. in diameter. In the right hand are irregular areas of decreased density. These areas are several millimeters in diameter. There is fusiform thickening of the soft tissues overlying those phalangeal joints which are obliterated.

Knees: All bones of the knee joints show bony atrophy, more marked in the left knee. The condyles of the femurs and the under surface of the left patella are irregular in outline. The under surface of the right patella shows slight lipping.

Feet: All the bones of the feet show atrophy (Fig. 2). This is most marked in the tarsi and metatarsi. The plantar arches are high. The articular ends of the heads of the first, second, third and fifth metatarsal bones of the right foot and the first and second of the left show varying degrees of destruction, some of them being almost completely destroyed. The outlines of the remaining portions of the articular ends of these bones present a scalloped appearance due to notching with more or less semicircular areas of complete destruction. There is irregularity in the outline of the articular surfaces of the bases of the outer four phalanges of both feet. There is a small area

Fig. 1.—Roentgenogram of the hands in Case 1.

of bony density lying just to the mesial side of the head of the fifth metatarsal bone of the right foot. The metacarpophalangeal joint space of each hallux is narrowed and the articular surfaces are decreased in density and irregular in outline. In the head of each first metatarsal bone is a focal area of decreased density. These two areas are nearly circular in outline, their diameters are about 4 mm. and their borders are not sharply defined.

SUMMARY OF ROENTGENOGRAPHIC FINDINGS

Atrophic changes involve all the bones of the hands, wrists, feet and knees. Destructive changes involve many of the bones of the hands. The terminal interphalangeal joints of both little fingers are normal. The third and fourth metacarpophalangeal joint spaces of the left hand are very slightly narrowed. All other joint spaces of the hands, wrists and feet are narrowed, obliterated or else distorted by position. There are slight proliferative changes about some of the joints. Focal areas of decreased density are found.

CASE 2 (Med. No. 5421).—J. G.; white, male, aged 57 years.

Diagnosis: Gout; arteriosclerosis; hypertension; chronic myocarditis; very questionable chronic nephritis.

The patient had used beer freely. He had had about sixteen attacks of severe polyarthritis of gouty character during the previous twenty-six years. Physical examination showed numerous tophi in the ears and on the fingers. The joints showed the changes of chronic arthritis. The radial artery walls were sclerosed. The blood pressure was 185 mm. systolic and 117 mm. diastolic. Otherwise physical examination was negative. The urine examinations were negative. Phenolsulphonephthalein excretion was 52 per cent. in two hours. The uric acid was 5 mg. and the nonprotein nitrogen 38 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

Roentgen Report (No. 8140).—Hands and wrists: There is moderate bony atrophy of the lower ends of the radii, ulnae, all the bones of the carpi, metacarpi and phalanges (Fig. 3). Proliferative changes involve most of the articular ends of the phalanges and of the distal ends of the metacarpals. The bones of the wrists show mottling, due to small areas of decreased and increased density. All the joint spaces of the wrists are narrowed and there is some irregularity in outline of the articular surfaces of the bones. The heads of the metacarpal bones, except the fourth metacarpals, of both hands show spur formation and more or less mottling. The metacarpophalangeal articular surfaces of the bones are irregular in outline, the articular margins show variable degrees of increased density and the corresponding joint spaces are narrowed. These changes are most pronounced in the metacarpophalangeal joint of the right middle finger, the articular surfaces being completely destroyed and replaced by an irregular density. The metacarpophalangeal joint of the right ring finger is normal except for slight narrowing of the joint space. The interphalangeal joints present various degrees of the same processes described in the metacarpophalangeal joints. Some of the interphalangeal joints are normal in appearance. Others, especially the proximal interphalangeal joints of the fourth and fifth phalanges of the left hand, are more or less obliterated and replaced by deposits of increased density with proliferative changes (lipping and spur formation). The shaft of the middle phalanx of the middle finger of the right hand is narrowed. There are numerous more or less circular, frequently fairly well defined focal areas of decreased density, localized mostly in the heads of the metacarpal and phalangeal bones.

The soft tissues of the fingers show irregular nodular thickenings. The larger arteries of the forearms and wrists are visible.

Knees: Proliferative changes involve the articulating surfaces of all the bones of both knee joints. There is lipping of the tuberosities of both femurs. The popliteal arteries and their larger branches are plainly visible.

Feet: The plantar arches are high. There is a moderate amount of bony atrophy of all the bones of the feet. The tarsal bones present a mottled appearance due to small areas of alternating increased and decreased density. The tarsal joint spaces are narrowed; some of them are obliterated and replaced by irregular lines of increased density. All these changes are more pronounced in the left foot. The heads of both first metatarsal bones are mottled. The margins of their phalangeal articular surfaces show lipping and the corre-

sponding joint spaces are narrowed. The head of the second metatarsal bone of the right foot shows proliferative changes. The heads of both fifth metatarsal bones are irregular in outline. The articulating surfaces of the bones forming the metatarsophalangeal joints of both fifth metatarsals are irregular in outline. There is partial subluxation of the bones of the fifth metatarsophalangeal joint of the right foot. The rest of the metatarsophalangeal joint spaces show varying degrees of narrowing. The interphalangeal joint spaces of the halluces are narrowed and there is lipping at the margins of the articular surfaces. Both great toes show a moderate degree of hallux valgus.

In the heads of both first, both fifth and the right second metatarsal bones are focal areas of decreased density. The latter tend to be circular in outline, the borders are more or less well defined and vary in diameter from 1 to 5 mm. The soft tissues in the regions of the first and fifth metatarsophalangeal

Fig. 2.—Roentgenogram of the metatarsals and phalanges of the feet in Case 1.

articulation of both feet show slight nodular thickening. The larger arteries of the feet are visible.

SUMMARY OF ROENTGENOGRAPHIC FINDINGS

The changes found are atrophic, proliferative and destructive in type. Certain bones and their joint surfaces are involved in these changes while others are normal or nearly normal. Some of the joint spaces are obliterated and ankylosis has occurred in certain of them. There is partial subluxation of one joint. There are focal areas of decreased density in some of the bones. The regions in which these areas occur usually show other bony changes. Nodular thickening of the soft tissues and arteriosclerosis of the larger vessels are present.

Case 3 (Med. No. 5471).—W. P. G.; negro; male, aged 43 years.

Diagnosis: Gout; questionable chronic nephritis.

The patient's habits were good. During the last ten years he had had a dozen attacks of gout affecting the joints of the lower extremities and of the phalanges of the fingers. On physical examination numerous tophi were found in the ears and about the finger joints. Otherwise physical examination was negative. The blood pressure was 135 mm. systolic and 95 mm. diastolic. The urine contained no casts, no blood and no epithelium. A scant trace of albumin was found once in the examination of several urine specimens. Phenolsulphonephthalein excretion was 42 per cent. in two hours. The uric acid was 4 mg. and the nonprotein nitrogen 44 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

Roentgen Report (No. 8225).—Hands and wrists: The radio-ulnar-carpal joint space of the left wrist is narrowed (Fig. 4). There is complete destruction of the distal end of the second phalanx and the proximal extremity of the terminal phalanx of the right little finger. The bony proximal and distal borders of the area of destruction form a curved line. The articular extremity of the terminal phalanx of the little finger of the left hand shows spur formation. The corresponding joint space is narrowed but the articular surfaces are smooth. The first phalanx of this finger shows a moderate degree of bony atrophy. In the index finger of the left hand the terminal joint space is obliterated. The first interphalangeal joint of this finger shows slight narrowing and there is slight lipping of the articular surfaces of the phalangeal bones. The major portion of the shaft of the second phalanx of this finger shows thickening at the expense of the medullary canal. The terminal phalanx shows proliferative changes. The terminal joint of the left thumb shows proliferative changes of the ends of the phalanges entering into its formation and there is slight narrowing of the joint space. The two phalanges of the left thumb show a moderate degree of bony atrophy. The remaining bones and joints of both hands and wrists are normal in appearance.

In the middle phalanx of the little finger of the left hand is a regular, circular area of decreased density 4 mm. in diameter. The bone immediately proximal to this area is increased in density, and just distal to it is decreased in density. In the proliferative changes of the terminal joint of the left index finger is an almost circular area of decreased density about 4 mm. in diameter. Similar areas lie proximal to it in the second phalanx and distal to it in the terminal phalanx of that finger. There is a well defined, circumscribed area of decreased density in the distal end of the first phalanx of the left thumb. In the proliferative changes on the palmar surface of this thumb is a clearly defined circular area of decreased density 3 mm. in diameter. At the base of the styloid process of the left ulna is a small, rather irregular, well defined area of decreased density. The soft tissues of the fingers show many nodular areas of thickening.

Feet: The first metatarsophalangeal joint of the right foot is narrowed, the margins of the articular surfaces are increased in density, and show proliferative changes. The inner margins of the head of the first metacarpal bone and the adjacent phalanx of the left great toe show slight irregularity in outline. The articular ends of the phalanges entering into the terminal joint of this toe show proliferative changes. The remaining bones of the feet show no proliferative changes.

The internal portions of the heads of both first metatarsal bones show moderately well defined, circular areas of decreased density from 2 to 4 mm. in diameter. Two similar areas are present in the proximal end of the first phalanx of the right hallux. One of these areas is 3 mm. in diameter and involves the joint surface. The other area is 2 mm. in diameter and is situated in the external portion of the bone near the proximal joint. Two small circular areas of decreased density are present in the internal cuneiform bone of the right tarsus. There are no changes in the soft tissues.

SUMMARY OF ROENTGENOGRAPHIC FINDINGS

Proliferative, atrophic and destructive changes are found. Not all the bones and joint spaces are affected. In the feet all the bones show slight atrophy but the proliferative and destructive changes are irregularly distributed. Many focal areas of decreased density are present. Most of these are in areas showing other bony changes. The soft tissues of the fingers show nodular thickenings.

CASE 4 (Med. No. 5297).—A. L. E.; white, male, aged 48 years.

Diagnosis: Gout; cirrhosis of the liver; questionable nephritis.

The patient had used large quantities of beer and whisky for many years. In the previous five years the patient had had five attacks resembling more the exacerbations of chronic arthritis than gout. Three of these attacks occurred in the Peter Bent Brigham Hospital. Physical examination showed several tophi in the ears. The joints of the hands showed some periarticular thickening. The radial arteries were palpable. Blood pressure was 156 mm.

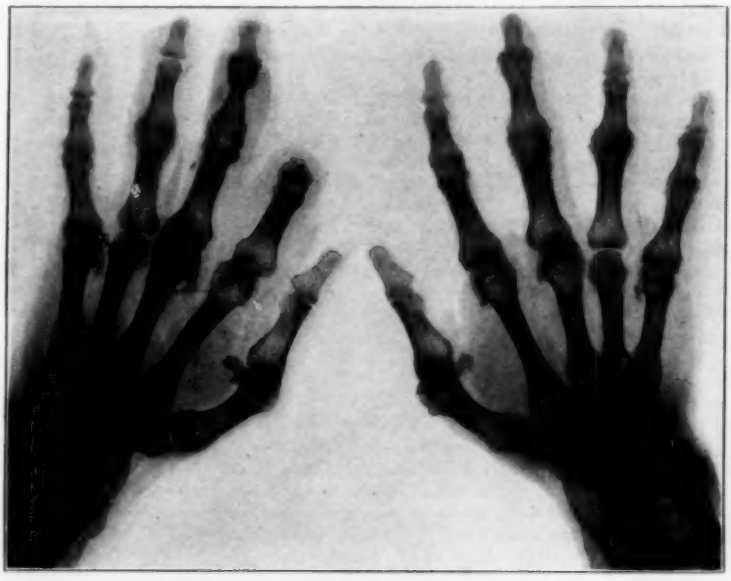

Fig. 3.—Roentgenogram of the hands in Case 2.

systolic and 96 mm. diastolic. The liver edge was palpable 4 cm. below the right costal margin. Otherwise the physical examination was negative. The urine showed occasionally a scant trace of albumin and a few casts. Phenolsulphonephthalein excretion was 24 per cent. in two hours. The uric acid was 5 mg. and the nonprotein nitrogen 53 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

Roentgen Report. (No. 1486).—Hands and wrists: The styloid processes of both ulnae are slightly irregular in outline. The joint spaces of both carpi are narrowed. The outlines of the carpal bones of both wrists are indistinct. The articular surfaces of the carpal bones of the right wrist show increased density. There is atrophy of the first metacarpal bone of the right hand. The

last two phalanges of the left little finger are atrophied, the interphalangeal joint is obliterated and shows proliferative changes. The terminal phalangeal joint of the ring finger of the right hand shows narrowing of the joint space and the articulating surfaces of the bones show lipping at their margins. The rest of the bones of the hand present no abnormalities.

In the right cuneiform bone is a well defined circular area of decreased density 1 mm. in diameter. Indenting the surface of the left metacarpal bone, just proximal to its head, is a small scalloped area of decreased density. Each styloid process contains a well defined, circular area of decreased density surrounded by normal appearing bone. In the outer margin of the proliferative changes in the left little finger is a well defined, circular area of decreased density 2 mm. in diameter. A similar area is present in the terminal phalanx of the ring finger of the right hand. The soft tissues show no changes.

SUMMARY OF ROENTGENOGRAPHIC FINDINGS

Localized proliferative and slight atrophic bony changes are found. The majority of the bones and joints of the hands and feet appear normal. Focal areas of decreased bony density occur.

CASE 5 (Med. No. 2929).—G. W. L., white, male, aged 68 years.

Diagnosis: Gout.

The patient had been a very moderate user of alcoholic beverages. For the past twelve years the patient had had monoarticular and polyarticular attacks of arthritis characterized by great swelling, deep redness, exquisite tenderness and extreme pain in the affected joints. On physical examination tophi were found in the auricles of the ears. From them sodium urate crystals were obtained. Large tophi were numerous in the fingers and about the elbow joints and on the posterior aspect of the right heel. Otherwise the physical examination was essentially negative. The urine showed the very slightest traces of albumin and a variable number of hyaline casts. Phenolsulphonephthalein excretion was 57 per cent. in two hours. Blood urea nitrogen was 19 mg. and uric acid 5 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

Roentgen Report (No. 210).—Feet: The bones of both feet show slight atrophy which is more marked in the left foot. There is narrowing of both the first metatarsophalangeal joint spaces. There are proliferative changes involving the margins of the articular surfaces of the bases of the phalanges and the heads of the metatarsal bones of these joints. The heads of the first metatarsal bones are wider than normal. There is partial subluxation of the phalanx entering into the formation of the right fifth metatarsophalangeal joint. The inner portions of the heads of the first metatarsal bones of both feet are decreased in density and present a mottled appearance. The latter appearance is due to numerous focal areas of greater decreased density. All the phalanges except half of the first are missing from the toe of the left foot. There is hallux valgus of both sides. The mesial outline of the head of each first metatarsal bone is indented with a semicircular area, about 4 mm. in diameter, of complete bony absence. The semicircular areas are situated in proliferative bony changes. The outer surfaces of the hands of both fifth metatarsal bones are irregular in outline and show circular, fairly well defined focal areas of decreased density. There is slight thickening of the soft tissues over the metatarsophalangeal joint of the left hallux and also over the second phalanx of the left little toe.

SUMMARY OF ROENTGENOGRAPHIC FINDINGS

There is generalized bony atrophy. Proliferative changes are localized to the first metatarsophalangeal joints. The majority of the joints appear normal. Well defined focal areas of decreased density occur. There is hallux valgus.

CASE 6 (O. D. D. No. 36014).—J. F. S., white, male, aged 42 years. Diagnosis: Gout.

The patient was a heavy beer drinker. He had had numerous attacks of monoarticular and of polyarticular arthritis of typical gouty character in the previous ten years. Physical examination was negative except for tophi in the ears, about the knuckle joints of the left hand and just above the olecranon processes of both ulnae. There were no evidences of cardiovascular disease. Blood pressure was 144 mm. systolic and 90 mm. diastolic. The urine contains no albumin but an occasional hyaline cast was found. Phenolsulphonephthalein excretion was 38 per cent. in two hours. The nonprotein nitrogen was 48 mg. and uric acid 6 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

Roentgen Report (No. 9216).—Hands and wrists: There is a moderate degree of atrophy of the lower end of the radius, ulna, the bones of the carpus,

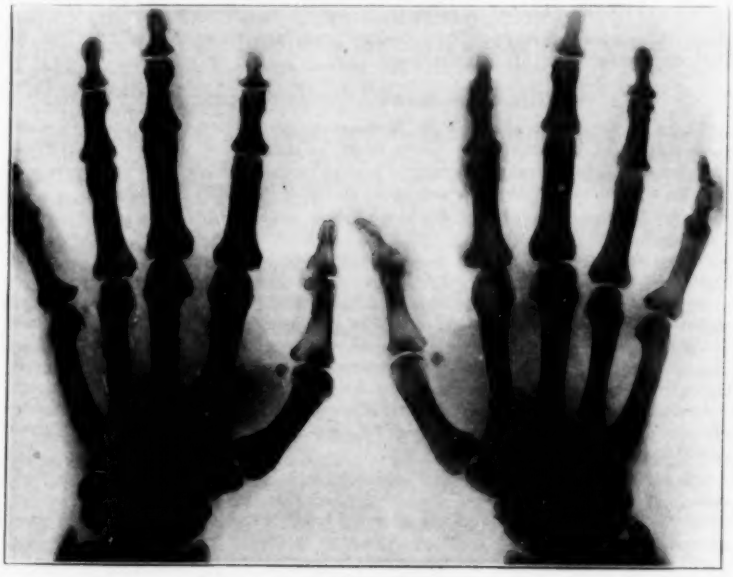

Fig. 4.—Roentgenogram of the hands in Case 3.

metacarpals and phalanges of the left hand. There is a very slight amount of atrophy of the bones of the right carpus and hand. The carpal joints appear normal. The inner margin of the base of the first phalanx of the right hand shows proliferative changes. The articular surfaces of the bones forming the right third metacarpophalangeal joint are in contact and their outlines are irregular. There are proliferative changes of the ends of both the bones of this joint. The middle finger of the right hand is a little shorter than the corresponding finger of the left hand. The other joints of the hands appear normal. In the head of the first metacarpal bone of the right hand is a small, oval area of decreased density. A similar area is present in the proliferative changes described in the base of the first phalanx of the right index finger. On the dorsum of the right hand is a nodular area of thickening of the soft tissues about 5 cm. in diameter.

Feet: All the bones of the tarsi, metatarsi and phalanges show a moderate amount of atrophy. All the tarsal bones show slight mottling. The bases of the third, fourth and fifth metatarsal bones of the right foot show mottling. The tarsal and tarsometatarsal joints are for the most part not clearly defined in the plate, probably due to position. Those which are outlined appear normal. The terminal joint spaces on each foot are distorted by position. The remaining joint spaces of the feet are normal in appearance. There are slight proliferative changes at the margins of the articular surfaces of the bones entering into the formation of the first metatarsophalangeal joint of both feet. The inner portion of the head of each first metatarsal bone shows proliferative changes and is decreased in density and irregular in outline. The left great toe shows slight hallux valgus. The mesial outline of each first cuneiform bone is scalloped due to notching with semicircular areas of decreased density. Similar changes are present on the mesial surfaces of the distal ends of the first phalanges of the halluces. In the proliferative changes described in the heads of the first metatarsal bones are small, more or less circular areas of decreased density. Two similar areas are found in the head of the fifth metatarsal bone of the left foot.

SUMMARY OF ROENTGENOGRAPHIC FINDINGS

More or less generalized bony atrophy occurs. There is a small amount of proliferative changes. One joint space is obliterated with irregularity of the joint surfaces. Most of the joints appear normal. Focal areas of decreased density are found. Nodular thickening of the soft tissues is present.

CASE 7 (Med. No. 6154).—F. J. S., white, male, aged 43 years.

Diagnosis: Gout; obesity.

The patient's habits were good. During the previous ten years he had had numerous attacks of arthritis in one or several joints of the lower extremities. Physical examination was essentially negative. There were no signs of cardiovascular disease. Blood pressure was 130 mm. systolic and 90 mm. diastolic. A tophus was present in the right ear and from it sodium urate crystals were obtained. The urine contained a scant trace of albumin, but no other pathologic elements were found. Phenolsulphonephthalein excretion was 50 per cent. in two hours. The uric acid was 5 mg. and the nonprotein nitrogen 44 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

Roentgen Report (No. 9454).—Hands and wrists: There are no bony changes.

Knees: Both patellae and the external tuberosities of the tibiae show proliferative changes.

Feet: There are slight proliferative changes of the margins of the articular surfaces of the bones forming the metatarsophalangeal joints of both halluces. All other joints are normal. The head of the left first metatarsal bone shows a localized area of decreased density in its mesial portion. The area is figure 8 shaped. Its long diameter is 12 mm. Its borders are only fairly well defined. There is hallux valgus and pes equinus.

SUMMARY OF ROENTGENOGRAPHIC FINDINGS

Slight proliferative changes affect the bones of the first metatarsophalangeal joints. A focal area of decreased density is found in the head of the left first metatarsal bone.

CASE 8 (Med. No. 10814).—P. A., white, male, aged 49 years.

Diagnosis: Gout.

The patient drank considerable quantities of wine. For the past eighteen years he had had one or two attacks typical of podagra every year. He was admitted to the hospital during the subsidence of an attack. On physical examination two small tophi were found in the auricle of the right ear. Sodium

urate crystals were obtained from them. There was some periarticular swelling and redness about the metatarsophalangeal joint of the right hallux. Otherwise the physical examination was essentially negative. The urine contained a slight trace of albumin and a variable number of casts. Phenolsulphonephthalein excretion was 38 per cent. in two hours. There were 6 mg. of uric acid per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

Roentgen Report (No. 14570).—Feet: There is slight narrowing of the metatarsophalangeal joint of the right great toe. There are slight proliferative changes of the margins of the articular surface of the phalanx entering into this joint. There are proliferative changes about a sesamoid bone just internal to the head of this metatarsal. All other bones and joints are normal. The head of the first metatarsal bone of the right foot on the mesial surface shows two small, well defined semicircular areas of decreased density about 3 mm. in diameter.

SUMMARY OF ROENTGENOGRAPHIC FINDINGS

There are slight proliferative changes and focal areas of decreased density in the head of the first metatarsal bone of the right foot.

CASE 9 (Med. No. 10684).—W. C. B., white, male, aged 61 years.

Diagnosis: Gout; chronic nephritis.

The patient's habits were good. For the past ten years he had had attacks of arthritis affecting the ankle joints, tarsal joints and at times the knees. Pain was present but resembled that of acute articular rheumatism rather than that of gout. He was admitted to the hospital with an arthritis of the left knee and right ankle. On physical examination small tophi were found in the auricles of the ears. From them sodium urate crystals were obtained. The heart was moderately enlarged to the left. The radial arteries were sclerosed. Blood pressure was 200 mm. systolic and 115 mm. diastolic. There was some swelling and tenderness of the left knee and right ankle. The urine contained a trace of albumin and a variable number of casts and leukocytes. Phthalein excretion rose from 5 per cent. in two hours to 14 per cent. during the patient's stay in the hospital. The blood urea nitrogen dropped correspondingly from 74 mg. to 56 mg. per 100 c.c. of blood. Uric acid was 8 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

Roentgen Report (No. 14369).—Knee: No abnormalities are found.

Feet: The heads of both first metatarsal bones and the first phalanx of the left hallux show small circular areas of bony absorption, from 1 to 2 mm. in diameter. The inner surface of the head of the left first metatarsal bone presents a mottled appearance. There is thickening of the soft tissues overlying the metatarsophalangeal joint of the left foot. No joint changes are present.

SUMMARY OF ROENTGENOGRAHIC FINDINGS

Focal areas of decreased density occur in the heads of the first matatarsal bones.

CASE 10 (Med. No. 10638).—A. S., white, female, aged 39 years.

Diagnosis: Gout, chronic nephritis, aortic insufficiency.

The patient had been a moderate user of alcoholic drinks. For the past five years she had had monoarticular and polyarticular attacks of arthritis characterized by great swellings, redness, exquisite tenderness and extreme pain of the affected joints. On physical examination small tophi were found in the auricles of the ears. From them sodium urate crystals were obtained. The heart was enlarged to the left. A diastolic murmur was heard loudest along the left sternal margin. The radial arterial walls were sclerosed. Blood pressure was 218 mm. systolic and 134 mm. diastolic. The metatarsophalangeal joints of both great toes were moderately enlarged. Otherwise the physical examination was essentially negative. The urine contained macro-

scopic blood due to menorrhagia and much albumin. The microscopic examination showed a variable number of hyaline casts. Phenolsulphonephthalein excretion was 36 per cent. in two hours. Nonprotein nitrogen was 53 mg. and uric acid 4 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

Roentgen Report (No. 14154).—Hands and wrists: The bones of the hands and wrists are normal.

Feet: The bones of the ankle joints and of the tarsi are normal. The heads of both first metatarsal bones show small, fairly well defined, circular areas of decreased density. Otherwise there are no abnormal findings.

SUMMARY OF ROENTGENOGRAPHIC FINDINGS

There are focal areas of decreased density in the heads of the first metatarsal bones.

DISCUSSION

Since the tophus is the only universally accepted pathognomonic sign of gout, for studies of that disease only those patients should be chosen in whom tophi are found and sodium urate crystals from them microscopically demonstrated. For this reason only those in which these requisities were fulfilled have been reported in the above protocols. A perusal of the protocols shows that in all cases the focal areas of decreased density which roentgenologists have considered as peculiar to gout were found. Similar changes were present in two other cases which were clinically gout, but in which no tophi were demonstrated. In another case without tophi, but which was clinically gout, the focal areas of decreased bony density were not found. The findings show that these areas are usually present in the bones of the wrists, hands, ankles or feet in gouty subjects.

Strangeways[4] has reported the finding of sodium urate in areas of decreased density which were demonstrated in the roentgenograms of the phalanges of gouty subjects. The roentgenographic appearance of the areas of decreased density as described by this writer show a complete absorption of lime salts and consequently are transparent. Similar areas are described in certain of the cases here reported and are most marked in Cases 2 and 3 (see Case Reports and Figs. 3 and 4). Strangeways also reported the findings of these transparent areas in cases which were typically "rheumatoid arthritis." All subsequent writers have apparently overlooked the work of Strangeways. They have assumed that the focal areas of rarefaction, the so-called gouty bony changes, were always due to the presence of tophi in the bones, and that they were diagnostic of gout. But these writers drew their conclusions from the study of the roentgen-ray findings in patients in many of whom tophi were not found. This detracts somewhat from the certainty that their cases were really gout. That these changes are always the result of tophaceous deposits may be questioned. As an indirect method of attacking the problem we examined the roentgen-

ograms of the bones of the wrists and hands, or the ankles and feet, or of all these regions in one hundred cases of chronic arthritis. These cases had not been diagnosed clinically as gout. They were chosen at random from the files of the roentgenographic department. In thirteen of these one hundred cases the focal areas of decreased density, the so-called gouty bony changes, were found and were fully as well defined as in the cases of true gout. Of the thirteen cases nine had been studied in the wards of the Peter Bent Brigham Hospital, one in private practice and three in the outdoor department of this hospital. In the first ten of these extensive clinical studies had been made and no clinical evidences of gout had been found. The findings are exemplified in Case 1. In three of the cases the amount of uric acid in the blood was determined and was not found to be increased above the normal. In six of the one hundred cases of chronic arthritis focal bony changes more or less closely resembling the focal areas of decreased density found in gout were demonstrated. These focal bony changes were differentiated from those occurring in true gout in that the degree of bony rarefaction was less complete, or the areas were less regular in outline, or their borders were less well defined. One of these cases had been studied in the hospital wards and the remainder in the outdoor department. In two of the one hundred cases of chronic arthritis focal areas of decreased density very irregular in outline or occurring in joint areas showing extensive bony destruction were found. One of these cases had been studied in the wards of the hospital.

These findings show that there are different types of focal areas apparently due to bony rarefaction in the radiograms of the anatomical parts examined in cases of chronic arthritis. Judging from their roentgenographic appearances there is no reason to believe that the factors producing the focal areas of bony rarefaction occurring in those cases are different from those occurring in cases of true gout. One plausible explanation for the production of certain of these bony changes is based on the work of Nichols and Richardson.[6] These investigators have shown that the inorganic salts may be absorbed from bone so as to produce changes detected by the roentgen ray which may not be obvious either macroscopically or microscopically. Focal areas of absorption of this character could produce the changes like those heretofore considered as resulting from the presence of tophi in the bones. That this is probably the explanation for the occurrence of many of these bony changes is indicated by the fact that we have been able to demonstrate the different types of these areas of focal absorption already described.

6. Nichols, E. H., and Richardson, F. L.: Arthritis Deformans, J. M. Res. **21**:149, 1909.

These areas appear to be but different degrees of the same process. Furthermore, a certain number of these areas occur within proliferative or destructive bony changes. Another factor that may play a rôle in the production of the focal areas of decreased density is that of pressure. These areas are often found in regions, such as the inner surfaces of the heads of the first metatarsal bones, which are subjected to pressure; or they may underlie large tophaceous deposits in the soft tissues. Our findings show that the focal areas of decreased density occur in from 10 to 12 per cent. of the cases of chronic arthritis which clinically are not gout. It should be noted that in many of these cases plates of both hands and feet were not available for examination. It is therefore probable that the changes are even more frequent than our figures show. If these changes are the result of tophi in the bones, then gout is far more frequent in its occurrence than heretofore has been suspected. Clinically, such frequency of the disease seems very improbable. These findings show that the focal areas of decreased density, the so-called gouty bony changes, found in the roentgenogram are most probably often not the result of tophi in the bones, but are frequently due to focal absorption of lime salts.

In one of our cases (Case 3) pus and sodium urate crystals could be expressed from a fistula in the little finger of the right hand. This fistula apparently connected with the area of bony absorption described in the two terminal phalanges of that finger. The area of absorption may have been due to urate deposits or it may have been the result of an osteomyelitis. The sodium urate crystals obtained from the fistula could either have come from a tophus in the bone or from tophi in the soft tissue through which it passed. In the middle phalanx of the little finger was a perfectly circular area of complete bony absorption, 4 mm. in diameter. This area may have represented a tophus. However, an area appearing exactly similar, except that it occurred in the edge of a metatarsal bone and hence was semicircular in outline, was found in a case without any clinical evidence of gout. These findings, together with those of Strangeways, seem to rule out the possibility of diagnosing tophi in the bones from the roentgenogram. In any event the areas of decreased density, the transparent areas of Strangeways, are of doubtful aid in diagnosing gout, unless the present clinical conception of that disease be changed radically.

Although the focal areas of decreased density found in gout occur in the other arthritides they are not wholly without diagnostic significance. They were present in the eighteen cases in which plates of both hands and feet were examined in the reports of Drinberg and Jacobsohn. These cases were clinically gout, although tophi were demonstrated in but three of them. If the three of our cases without

tophi are considered as true gout, then all but one of the cases here reported showed the focal areas of bony rarefaction, the so-called gouty changes. If only those cases in which tophi were demonstrated are to be accepted as true gout, then all the cases so far reported, including our own, in which there were roentgenograms of both hands and feet available for examination have shown the changes. Our one case without tophi in which the bony changes did not occur had an attack of podagra while under observation. The blood uric was persistently high and the nonprotein nitrogen within normal limits. Therefore, this case was probably one of gout. The findings of other observers together with our own show that the focal areas of decreased density, heretofore considered as peculiar to gout, are rarely absent in that disease. Their absence would be some evidence against the existence of gout in a given case. On the other hand their presence is no more than suggestive of gout, since they are found in from 10 to 12 per cent. of cases which clinically are not gout.

Strangeways found a type of nongouty arthritis in which the roentgenographic changes exactly corresponded to those of gouty arthritis. Other investigators have paid but scant attention to the type of arthritis occurring in gout. A perusal of the roentgenographic findings in the case reports here presented shows that a variety of radiographic changes are found in the bones and joints of the hands and feet of gouty subjects. These changes may be divided into the four following groups which more or less overlap each other.

1. The focal areas of decreased density may be the only changes found (Case 10). These changes are usually most pronounced in the heads of the metacarpal or metatarsal bones.

2. Besides the focal changes just mentioned very slight lipping at the margins of the articular surfaces of the bones entering into the first metatarsophalangeal joint occurs (Cases 7 and 8).

3. In addition to the changes noted above either a variable degree of atrophy of all the bones of the affected member occurs (Case 5) or largely of only the bones of an involved joint (Case 6).

4. In addition to all the above changes narrowing of certain joint spaces with marked proliferative and atrophic changes occur (Case 2; Fig. 3).

A striking peculiarity of the arthritis is that only certain joints are affected while others remain normal (Cases 2, 3, 4, 5, 6, 7 and 8). The one exception to this statement is found in the feet of Case 2. Here, although all the joints are involved, some are but little affected. A second characteristic is that where there are marked changes in a joint the bones entering into its formation show atrophy (Cases 2, 3, 4, 5 and 6). This atrophy may be limited to these bones, or it may be

generalized in the member affected. The cause for bony atrophy, when present, is somewhat problematical. It may have been due in part to the pressure of the large tophaceous areas in some cases (Cases 2, 3, 5 and 6). It may have been the result of the lack of use of the affected members, the so-called atrophy of disuse. These two characteristics are not mentioned by Strangeways in his report. However, judging from the plates accompanying his article they were present. A third characteristic is that in the seven cases in which arthritis was present one or both metatarsophalangeal joints of the great toes were involved in all but one case (Case 4). In this case questionable lipping at the margins of the articular surfaces of the heads of both first metatarsal bones was present. Hallux valgus occurred in two of these cases (Cases 2 and 7), and was present to a slight extent in one great toe of a third (Case 6). This may explain the arthritis in these three cases. In the other four cases no cause except that of an arthritis due to gout was evident. It should be emphasized that this region of the foot is subject to more or less trauma, but the rôle it played in producing the arthritis cannot be ascertained. On the other hand, this is the most frequent region in which attacks of gouty arthritis occur. A striking feature of the arthritis in the five cases showing the most marked changes was the almost invariable symmetry in the two hands or feet of the bones and joints affected. The so-called Bruce's nodes are well shown in one case (Case 2; Fig. 3). Strangeways has demonstrated that these nodes are bony exostoses and not sodium urate deposits. They are not diagnostic of gout. The most extensive bony and joint changes were present in the case (Case 2) in which gouty attacks had occurred over the longest period of years. This relation between time and the extent of these changes was not present in the other cases.

A comparison of the different types of gouty and nongouty arthritis is instructive. The bony and joint changes in radiograms of the nongouty arthritides very largely fall into the three following classes:

1. A class characterized by proliferative changes at the margins of the articulating surfaces of the bones and a negligible amount of bony atrophy. In radiographic literature this class is called hypertrophic arthritis.

2. A class characterized by generalized bony atrophy without destructive changes of the joint surfaces. No proliferative bony changes occur. There is fusiform thickening of the soft tissues about the joints. Roentgenologists designate this class as atrophic arthritis.

3. A class characterized by proliferative and marked atrophic bony changes. This type of arthritis is the one accompanying demonstrable infections of the joints. It is known as the infectious type of arthritis in roentgen-ray literature.

Focal areas of decreased density, resembling those found in gout, occur in all types of nongouty arthritis. But focal areas of decreased density without any other bony or joint changes have been found only in gout. This may be because of the lack of material for examination, since relatively few cases of early nongouty arthritis have been available for examination. The second gouty group resembles the hypertrophic type of nongouty arthritis. The third and especially the fourth groups fall into a peculiar class. In character their changes resemble the infectious type of nongouty arthritis. In the actual appearances in the roentgenograms, however, a striking difference between the two types of arthritis is usually manifest. This is because of the sharply localized, extreme degree of bony atrophy which occurs in the infectious type of nongouty arthritis. However, of the latter type roentgenograms have been found which closely resemble the atrophic and proliferative changes occurring in gout. One of these cases (J. O., Med. No. 11125) was studied in the hospital wards. Although particularly sought for, no clinical evidences of gout were found. The blood uric acid was 1.3 mg. per 100 c.c. of blood. From the above discussion together with the results of Strangeway's investigations, it is evident that there are no bony or arthritic changes in the roentgenograms which are diagnostic of gout.

SUMMARY AND CONCLUSIONS

The findings in the work here reported show that a type of arthritis may occur in gout which presents an unusual appearance in the roentgenogram. Nevertheless, roentgenographic findings in even the most characteristic type of gouty arthritis may be resembled so closely by nongouty arthritis that such findings cannot be considered as more than suggestive of the diagnosis of gout. The focal areas of decreased density in the roentgenogram which roentgenographers consider to be due to tophi are probably very often merely focal areas of absorption of lime salts. These focal areas are found in from 10 to 12 per cent. of the nongouty arthritides and are, therefore, not diagnostic of gout. Their absence is of more diagnostic value than their presence, since they are almost invariably found in some of the bones of the wrists, hands, ankles or feet in true gout.

We wish to thank Dr. G. W. Holmes, chief of the Roentgenographic Department of the Massachusetts General Hospital, Boston, for criticisms and suggestions.

CORRECTIONS IN ARTICLE ON SINO-ATRIAL BLOCK

To the Editor:—In the article on "Sino-Atrial Heart Block in a Child," Arch. Int. Med. **24**:458 (Oct.) 1919, there has been an error in the order of the figures. On page 465 the upper of the three cuts should be the lower and belongs with the legend of Figure 14. The middle cut of the three should be the upper and belongs with the legend of Figure 12. The lower cut should be in the middle and belongs with the legend of Figure 13.

On page 467 there are additional errors which will result in much confusion unless the reader appreciates the fact that the references to illustrations are incorrect.

Page 467, Line 16: "Fig. 11" should come after "four blocks occur in succession."
Line 17: "Fig. 11" should read "Fig. 12."
Line 18: "Fig. 12" should read "Fig. 13."
Line 26: "Fig. 13" should read "Fig. 14."
Line 33: "Fig. 14" should read "Fig. 15."
Line 49: "Figs. 15 and 16" should read "Figs. 16 and 17."

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